CLINICAL PELLAGRA

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Affectionately and gratefully dedicated
to my eldest brother

JAMES COFFEE HARRIS, A M

Educator and Philosopher

who up to the day of his death in his eighty third year
had the clearest head and
the purest merriest heart
of any man known to me
He taught me in my youth
both by precept and example
to seek truth always
to tell the truth without fear of consequences
and to respect the opinions of recognized authorities
but that one should have the courage
to express his own views
when based upon conclusions
arrived at independently
after careful study and mature deliberation

FOREWORD

Now that at least a dozen clearly defined pathologic states in man and animals have been found to respond in a dramatic way to the administration of one or another of the simple chemical substances which are essential nutrients and which are supplied by an adequate dietary, there is a tendency to over simplify our reasoning about some of the nutritional deficiency states This was inevitable because in the earlier years of nutritional research both theory and experiment were largely in the hands of biochemists Pathologists and clinicians with few exceptions were not interested, and whenever they were they lacked the kind of knowledge which is essential for the discovery of the cause and the nature of the factor involved in the etiology of the "deficiency diseases" The first phases of the investigation of nutritional deficiencies could be solved only by biochemists Their studies were necessarily handicapped for want of knowledge which lies within the province of medically trained persons Happily this period is now history and the clinician, versed in the pathology of disease, is making his invaluable contributions to the science of nutrition

The book, *Clinical Pellagra*, prepared by a close student of pellagrous patients and of the scientific contributions which have thrown light on the nature of the disease, assisted by several distinguished scientists, presents a searching inquiry into the interaction of several agencies secondary to specific dietary deficiencies, which offer a plausible explanation of the complex manifestations with which the clinician meets in pellagrous patients, and particularly in pernicious anemia and sprue

The title hardly does justice to the book It is a philosophic treatment of clinical and experimental data of many kinds, contributed by many able workers who have contributed to the development of our knowledge of the biochemistry of nutrition and of the biologic agencies which act in conjunction with malnutritional states to undermine and pervert physiologic functions of certain types Nowhere else is so complete a history

of investigations relating to pellagra, and the assembled quotations and comments make a fascinating story. Clinicians will be entertained and instructed by reading the views of their studious colleague, which point out how, as the result of primary deficiencies, bodily conditions may through debility and derangement of function of the gastrointestinal tract and the liver become unable to utilize indispensable nutrients in an adequate dietary. The book is a distinct contribution in that it extends the deficiency disease viewpoints beyond simple chemical reasoning into the field of perverted physiologic function.

E. V. McCOLLUM

PREFACE

I have endeavored to write a factual treatise on pellagra, in which the various phases of the subject are discussed, including summaries of the most important contributions by those who may be regarded as authorities on the subject. In the chapters on the Genesis of Pellagra and on Pellagra, Pernicious Anemia and Sprue my own views have been expressed for what they are worth. I do not make any claim to originality in my ideas on pellagra, my conclusions regarding the genesis of pellagra have been formed from reading the published articles on studies and investigations by others. There seems to be sufficient evidence to conclude that the essential factor in the production of pellagra is a deficiency of nicotinic acid, the pellagra preventive factor in vitamin B, an enzyme activator, but the underlying pathogenesis of the nicotinic acid deficiency, in a large proportion of cases, probably is insufficiency of the stomach and liver.

While in the last few years much brilliant work has been done on the etiologic factors in pellagra by Goldberger, Sebrell and their associates, Ruffin and Smith and their associates, Spies and his associates, and many others, I believe that Sydenstricker, in his gastric intrinsic factor hypothesis and in his suggestion that liver pathology plays an important part in the genesis of pellagra, is thinking and working in the right direction towards the final solution of the basic underlying causes of the disease.

Attention is called to the chapters in this book by Ruffin and Smith and by Sydenstricker for discussions on the recent advances in the study of pellagra, particularly the use of nicotinic acid in its treatment. No more important contributions to the literature on pellagra have been made than may be found in the chapters summarizing the investigations on pellagra at Duke University Hospital, Durham, North Carolina and the University Hospital in Augusta Georgia.

The work of Porter and Higginbotham on the heart in pellagra is an outstanding scientific contribution to the study of the disease. I desire to express my gratitude for the privilege

of reproducing the article published in the Southern Medical Journal by Porter and Higginbotham as a chapter in this book

With the consent of the authors, and the publishers of *The Journal of Laboratory and Clinical Medicine* a chapter by Sutton and Ashworth of Northwestern University Medical School, Chicago, on the interrelations between vitamin and hormone deficiencies is included

The literature on pellagra in children is scant, and the chapter on "Pellagra in Childhood" by Dr Katharine Dodd, Associate Professor of Pediatrics in Vanderbilt University, is commended to pediatricians and to general practitioners who may be called upon to treat juvenile pellagrins

I am profoundly grateful to Dr E V McCollum, Professor of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, for reading the manuscript of this book and for his Foreword

This book could not have been written had it not been for the fact that my son, Seale Harris, Jr, has been willing to bear the burden of carrying on the work of the Seale Harris Clinic for a large part of the time during the three years required in its preparation Seale Harris, Jr, has assisted me in the preparation of various chapters

Dr Larry Shipp, formerly of the Seale Harris Clinic, abstracted many articles on pellagra Dr Max Emmert, Jr, of the Seale Harris Clinic and James Crenshaw, a medical student in Washington University, have aided greatly in assembling the bibliography

Finally, the author desires to express his appreciation to the efficient clerical staff of the Seale Harris Clinic, Miss Ruby Albright, Miss Ruth Wright, and to Miss Virginia Luna in particular, for the typing which they have done during the preparation of the manuscript

SEALE HARRIS

BIRMINGHAM ALA

CONTENTS

SECTION I

HISTORY AND EPIDEMIOLOGY

CHAPTER I

CHAPTER II

CHAPTER III

SECTION II

THE QUEST FOR THE CAUSE OF PELLAGRA A HISTORICAL REVIEW

CHAPTER IV

PAGE

SECTION III

ETIOLOGY AND PATHOLOGY

CHAPTER X

CHAPTER XI

CHAPTER XII

CHAPTER XIII

SECTION IV

CLINICAL INVESTIGATIONS

CHAPTER XXIII

CHAPTER XXIV

CHAPTER XXV

SECTION VI

PROPHYLAXIS

CHAPTER XXVI

CHAPTER XXVII

CHAPTER XXVIII

SECTION VII

TREATMENT

CHAPTER XXIX

PAGE

CHAPTER XXX

CHAPTER XXXI

ILLUSTRATIONS

FIG PAGE

COLOR PLATES

CLINICAL PELLAGRA

CLINICAL PELLAGRA

INTRODUCTION

When the late George Searcy recognized the first outbreak of pellagra at Mount Vernon, Mobile County, Alabama, in 1906, there were only a few brief references to the disease in the English literature It is believed that practically the only reference of importance, available to George Searcy when he made the diagnosis of pellagra in 1906, was an encyclopedic article, in a two volume English medical dictionary called *Lexicon Medicum,* the first edition of which was published in London in 1829 This encyclopedic dictionary was edited by Robert Hooper, and an American edition, revised by Samuel Akerly, was published by Harper Brothers in 1845 Hooper, in his *Lexicon Medicum,* states that there was little available data in English on what, in 1829, was called "pelagra," which he considered as the analogue of "elephantiasis italica" He quoted verbatim the 1,500 word description of the symptoms and course of "pelagra" which he says was "extracted from a treatise on this singular disease by Dr W X Jansen (1788) who had seen cases in Milan" It may be added that there is no more accurate description of the severe cases of pellagra in medical literature today than that published by Jansen one and one half centuries ago

Books on Pellagra —To meet the need for authentic information on the new disease, which was becoming a serious problem in the South in 1910, Claude Lavinder, past assistant surgeon of the United States Public Health Service, and J W Babcock, Columbia, Superintendent of the South Carolina State Hospital for the Insane, translated the book on *Pellagra* by the celebrated French neuropsychiatrist, Dr A Marie, of Paris Marie frankly stated that he had "borrowed" from Professor Cesare Lombroso "the essential points for the writing of this book, which is but a feeble reflection of the enormous labor of a lifetime by Lombroso" Marie gives credit to Theophile

Roussel, one of his French confreres, for "having so completely delivered his country (France) from this scourge (pellagra, 1842 1866), that even before his death the people had almost lost the memory of it" It is interesting to note that France was delivered from the ravages of pellagra by abandoning the use of maize (corn) as a food What Marie said regarding the *improvement in living conditions in* Southern France *after the* inhabitants of that region had abandoned the use of corn products in their diets should be considered by those who desire to eradicate endemic pellagra from the United States Marie said "The industrial improvement among the people has completed the work of liberating France from the use of a cereal (corn) now abandoned to animals"

Lavinder and Babcock interpolated the text of their translation of Marie's book on *Pellagra* with many notes on various phases of the new disease as observed by themselves and other Southern physicians This book had a profound influence on the opinions of physicians who were treating pellagra, and since it propounded the Italian hypothesis of the genesis of pellagra, the maize theory of pellagra was generally accepted

For a decade after pellagra was found to be endemic in the South, it was the most debated and discussed subject at every local and state medical meeting held in the South, and a number of Southern clinicians, including myself, who had published *many articles on pellagra, had the laudable ambition to write* a book on the subject In the year 1912 three books on pellagra were published, and they covered the subject so thoroughly that probably a dozen physicians abandoned their authorship plans

Stewart Roberts, of Atlanta, in 1910, before writing his comprehensive monograph on pellagra, went to Austria and Italy where he studied the disease as it existed in those countries Roberts' book on *Pellagra,* published in 1912, dealt with the history and pathology of the disease more thoroughly than any book that had been published up to that time An able, scientific and practical clinician, Stewart Roberts knew how to meet the needs of the general practitioner, and his book was a most popular treatise on pellagra

Edward Jenner Wood, of Wilmington, chairman of the Pellagra Commission of the North Carolina Board of *Health,* pub

lished *A Treatise on Pellagra for the General Practitioner* (D Appleton Century Company) in 1912 Wood's review of the American literature on pellagra was comprehensive, and from the viewpoint of diagnosis and treatment his book was particularly valuable

George M Niles, of Atlanta, published a book on *Pellagra* in 1912 (W B Saunders Company, Philadelphia) Niles covered the clinical aspects of the disease in a practical way, without attempting to review the foreign literature on the subject

William H Deaderick and Lloyd Thompson, of Hot Springs, Arkansas, published a book on *Endemic Diseases in the South* (W B Saunders Company) in 1916 Deaderick previously had written an excellent monograph on malaria which was widely read in the South Deaderick and Thompson's chapter on pellagra epitomized the work that had been done on pellagra in the South, and it was a valuable contribution to the literature on the subject

H F Harris, of Atlanta, a highly trained pathologist and linguist, and state health officer of Georgia, began preparing his book on pellagra in 1908, and after ten years of intensive study of the disease, including a prolonged visit to Italy, he completed the most thorough and the most comprehensive treatise on pellagra that has been published in any language H F Harris' monograph on pellagra was published in 1919 (The Macmillan Company, New York), and today it contains more authentic information on the history of pellagra than can be found elsewhere in all medical literature No clinical investigation on pellagra should be undertaken without reading H F Harris' book to learn what has been done by European pellagrologists H F Harris showed that some of the theories on the etiology of pellagra, which were announced as original in the United States, duplicated the ideas of a number of Italian pellagrologists in their one hundred and fifty years' study of the disease

Though much progress has been made in the study of pellagra in the last two decades, no other book on the subject has been published since the monumental monograph of H F Harris appeared in 1919, and that book has been out of print for many years It therefore seems timely to prepare, for general prac

titioners and public health workers in particular, a treatise on a disease that has become a national problem

Personal Potpourri—The study of pellagra has been an intriguing subject to me since the latter part of November, 1906, when I assumed the duties of Professor of Medicine in the Medical Department of the University of Alabama On arriving in Mobile I found my confreres in the medical school excited over the outbreak of pellagra, a new disease in Alabama at the Alabama State Hospital for Insane Negroes located about 40 miles from Mobile Several members of the faculty had been invited to Mount Vernon to see the patients, and Eugene D Bondurant, professor of neuropsychiatry, had been the first one called upon to study the disease

A few days after my arrival in Mobile I was invited by Dr E L McCafferty, the physician in charge of the Negro Insane Hospital, to examine the 50 or more pellagra patients then under his care and to offer suggestions on the diet and treatment of his patients It is interesting to recall that I was impressed with the emaciation of the victims and advised forced and frequent feedings of milk, eggs, meats, vegetables, and other highly nutritious foods—the then, and now, recognized treatment of pulmonary tuberculosis Dr McCafferty said that he had already placed his pellagrins on just that diet, on the advice of Drs James T Searcy, then Superintendent of the Alabama Insane Hospitals, George H Searcy of Tuscaloosa, E D Bondurant, Herbert P Cole, Instructor in Gynecology, and W Gilman Winthrop Instructor in Surgery in the Mobile Medical School, all of whom had seen the patients several weeks or months before I saw them Cole and Winthrop (1906) at the time were giving transfusions to the emaciated victims of pellagra, which, combined with diet, had decreased the mortality very materially among the negro insane at the Mount Vernon Hospital

After examining the patients, who months before had been diagnosed as having pellagra, I had to admit that I had no knowledge of the disease until I heard it discussed by my confreres on the faculty of the Medical Department of the University of Alabama Before going to Mobile, I spent a year in postgraduate work, six months of which was spent in Johns

Hopkins Medical School, where I had the privilege of attending daily ward rounds conducted by Barker, Thayer, McCrae, Futcher, Hammon, and Boggs in the Johns Hopkins Hospital, and none of that group of great clinicians had discussed pellagra. Parenthetically the opinion may be added that if there had been even a few cases of so distinct a disease entity as pellagra in the Johns Hopkins Hospital before 1906, Osler, Welch, or some of the junior group mentioned would have recognized it.

During six months of visiting and working in the clinics of Berlin, Vienna, and other European cities in 1906, pellagra was not mentioned by any clinician. I later learned that Neusser, Professor of Medicine in the University of Vienna, had studied pellagra in the Austrian Tyrol and in Rumania, and that his monograph on pellagra published in 1887 was one of the most important contributions to the literature on the disease, but during three months while I was studying under Neusser's assistants in the internal medicine wards of the Allgemeines Krankenhaus, a 2,000 bed hospital, no case of pellagra was seen, nor was the disease discussed. In 1906 Adolph Schmidt, then of Dresden, who later succeeded Neusser as professor of medicine in the University of Vienna, was the outstanding clinician in the world on intestinal diseases. It was in the Dresden General Hospital that Schmidt worked out his test diets in intestinal diseases, and he had under his care a large number of patients with intestinal diseases, many of them with diarrhea but none resulting from pellagra. It seems unlikely that there could have been cases of pellagra in the hospitals of Berlin, Dresden, or Vienna, or some of the great authorities in medicine in those cities would have called attention to so distinct a disease when teaching American physicians then in postgraduate work in Europe.

The Gulf States Journal of Medicine and Surgery.—In 1908 I purchased the *Mobile Medical and Surgical Journal,* and became its editor. Associated with me as co-editor was one of my confreres, Dr. H. A. Moody, Professor of Therapeutics in the University of Alabama. This journal was enlarged and its name changed to the *Gulf States Journal of Medicine and*

Surgery with an announced policy to devote its columns largely to publishing papers on tropical diseases by physicians in the Gulf States

In 1910, when the *Gulf States Medical and Surgical Journal* was merged with the *Southern Medical Journal*, then published at Nashville, I became secretary of the Southern Medical Association During the next decade pellagra was the topic of more papers, discussions, and editorials in the *Southern Medical Journal* than any other half dozen diseases The proceedings of the Gulfport Pellagra Conference in 1908 were published in the *Gulf States Medical and Surgical Journal* This was the first time in the United States that an entire number of a medical journal was devoted to the publication of papers on various phases of the pellagra problem

The Southern Medical Association and Pellagra—It is a coincidence that in 1906, the year that pellagra was recognized as epidemic in the Alabama Insane Hospital for Negroes, the Southern Medical Association was being organized by a group of physicians who had been members of the House of Delegates of the American Medical Association that year Dr George C Savage, of Nashville, one of the outstanding ophthalmologists of his time, suggested the need for an organization of Southern physicians Then Dr H H Martin, an eminent otolaryngologist of Savannah, President of the Georgia State Medical Association, with Dr James M Jackson of Miami, President of the Florida State Medical Association, Dr W W Crawford, President of the Mississippi State Medical Association, and Dr Oscar Dowling, President of the Louisiana State Medical Association, and Dr Jere Crook, representing the Tennessee State Medical Association, proceeded to organize the Southern Medical Association To Dr Martin was delegated the duty of arranging for a meeting to be held in Chattanooga, Tennessee, conjointly with the Tri State Medical Society of Tennessee, Georgia, and Alabama, in November, 1906 Drs Martin Crawford, and Crook persuaded the leaders of the Tri State Medical Society to merge that organization into the Southern Medical Association

At the next meeting of the Southern Medical Association in Birmingham in 1907, I was elected chairman of the section on

medicine The year following (1908), in my address, I selected a subject which at that time was in the minds of many Southern physicians, *i e*, "Problems in Medicine Which Affect the Prosperity of the South" I mentioned the four diseases, malaria, the most prevalent of all diseases in the South, yellow fever, which had been epidemic in the South in 1904, hookworm, then the absorbing medical problem, and pellagra which had been found to be endemic, and epidemic, in the South in 1906 I suggested that while the Southern Medical Association had been organized primarily and solely as a scientific organization it should become the clearing house for information on, and for the discussion of, the endemic tropical diseases which affected the welfare of the South A section on public health in the Southern Medical Association was organized by me, and it received the enthusiastic support of the public health officials and the general practitioners of all the Southern states

Pellagra increased so rapidly in the rural districts of the South and in hospitals, orphanages, and penitentiaries—in the same regions in which malaria, uncinariasis, typhoid fever, and amebiasis prevailed—that for a number of years in the sections on medicine and public health of the Southern Medical Association pellagra was the most important topic for papers, symposiums, and discussions The Association's journal, the *Southern Medical Journal*, became the principal medium through which the rapidly accumulating knowledge of the clinical and public health aspects of the pellagra problems was disseminated among the physicians in the South

Our Debt to Goldberger—Many of my pellagra patients have come from intelligent and prosperous families, in the rural districts, in whom it seemed that diets deficient in proteins could not have been the only factors in producing the disease Physicians from every Southern state have expressed the same opinion Therefore, I never accepted Goldberger's now abandoned theory that pellagra is due solely to an unbalanced diet, deficient in proteins (certain amino acids) I believe ardently in vitamin deficiencies as the cause of many diseases, and I am convinced that the pellagra preventive factor in vitamin B, now believed to be nicotinic acid, is the essential etiologic factor in pellagra I believe, however, that intrinsic factors in the stom

ach and liver are underlying causes of nicotinic acid deficiency, and that there are many predisposing causes of the disease. Though I have disagreed with Goldberger's views and methods in many respects, I assert that the outstanding work in the study and prevention of pellagra in the twentieth century should be credited to the late Joseph Goldberger of the United States Public Health Service.

Goldberger spent the best years of his life in the study of pellagra and in constructive efforts to prevent the disease. The promulgation of Goldberger's "unbalanced diet" theory of pellagra among the farmers of the South stimulated them to diversified farming and toward improving the food supply in the rural districts, and, no doubt, he should be credited with having done more towards reducing the incidence of pellagra than any other man.

Early Experiences in Treating Pellagra.—The Mobile City Hospital was utilized for clinical teaching by the faculty of the Medical Department of the University of Alabama and, having been professor of medicine, I became the physician in chief of that all charity institution. There were no cases of pellagra in the Mobile City Hospital in 1906, and no one connected with the institution could remember having seen any case that resembled those which most of the faculty had seen in the hospital for the insane at Mount Vernon, forty miles away. In 1907 a few patients were admitted, and for a number of years there were cases largely among the negroes who resided in the sections of the city in which open privies were in use. At no time, however, was pellagra a problem among the negroes of Mobile as compared to the ravages of tuberculosis.

In my private practice in Mobile from 1906 to 1915, I treated many patients with pellagra sent to me from the rural districts of southern Alabama, southwest Mississippi, and western Florida. Many of these patients were from prosperous families, merchants and planters in particular. Many of them had the money to pay for a month or six weeks' stay in private hospitals, where they were given the Weir Mitchell rest cure with forced feedings low in carbohydrates, particularly green vegetables, and high in meats, eggs, milk, and other foods of high protein content. In addition, the rooms were kept darkened

I, like every other physician of my acquaintance in the early pellagra days, believed that malnutrition was a predisposing cause, but not the only etiologic factor in pellagra, and that building up the nutrition of the pellagrin was the most important indication in prevention and treatment. I cannot recall losing a patient with pellagra in my private practice during the years that I lived in Mobile except one man, a banker, who left the hospital apparently cured clinically. A few days later after having been exposed to the sun for two hours on a hot summer's day, the dermatitis, diarrhea, and mental depression returned, and this patient committed suicide.

It should be remembered that many of the private patients were from families who could afford to have proper treatment and could follow the proper diet after returning home, and that in private practice the very poor who were prone to the malignant types of the disease were not seen. The low mortality rate in pellagra in my practice is in line with that of other physicians in private practice, except in the first reported epidemics. Dr. J. R. Williams, of Houston, Mississippi, recently said that he had lost only one pellagra patient out of more than one hundred cases, and that was his first patient. Many physicians throughout the South have reported large series of cases treated successfully without the loss of a patient. Goldberger said that the mortality of pellagra should not be over 2 per cent of those treated properly. The high mortality rates from pellagra come from insane hospitals, almshouses, and charity hospitals in which aged pellagrins, defectives, dependents, and derelicts would have died of pneumonia, senile dementia, tuberculosis, cardiovascular renal disorders, or other degenerative diseases if they had not succumbed to pellagra.

Recent Investigations.—Clinical investigations and experimental studies during the last decade have resulted in many important advances in the knowledge of pellagra. Sebrell and his associates in the United States Public Health Service have continued the studies begun by Goldberger on vitamin deficiency in dogs. Other important contributions have been made by Sydenstricker at the University of Georgia, Ruffin and Smith at Duke University, Porter at the Medical College of Virginia, Mulholland and John Staige Davis at the University of Vir-

ginia, Spies and Blankenhorn in Cleveland and Cincinnati, Spies, J B McLester, J S McLester, and Grosbeck Walsh in Birmingham, Roy Turner at Tulane University, John Youmans and Katharine Dodd in Vanderbilt University Medical School, and many other clinicians, including a number of general practitioners in rural districts

The culmination of this decade of research was the epoch making discovery of Elvehjem and his associates in the University of Wisconsin (1937), who found that nicotinic acid and nicotinic amides, normally present in the liver, will cure black tongue in dogs, and they suggested its use in human pellagra Following the publication of Elvehjem's suggestion, almost simultaneously, a number of investigators, including Ruffin and Smith at Duke University, Durham, North Carolina, Spies and J B McLester in Birmingham, Sydenstricker at Augusta, Georgia, Fouts, Lepkovski, Helmer and Jukes at the University of Indiana, began the use of nicotinic acid in human pellagra

The dramatic cures of pellagra by the use of nicotinic acid in more than a thousand reported cases have revolutionized the treatment of pellagra and its use has opened up new fields of investigation on the etiology of pellagra, which may result in changing some of our concepts regarding the genesis of the disease Considering the accumulated knowledge of pellagra even in the last decade, it would seem that the time is propitious to collect and correlate these data and condense them into a volume for the use of those who deal with the disease

The Quest for the Cause of Pellagra—"It is not who is right, but what is right" that should be considered when there is a difference of opinion on any controversial subject I believe, with many other physicians, that all the factors in the etiology of pellagra have not been discovered, and one of my reasons for writing this book is the hope that some of the facts presented, which others have brought out in their studies of pellagra, may stimulate further investigations on all phases of pellagra

It has been a pleasant task to record the data regarding the researches and clinical studies that have been made by Southern physicians in their earnest efforts to aid in solving the pellagra problem I have tried to present, without bias, the various theories on the etiology of pellagra and the reasons why the pro

ponents of various theories believe in them So many theories have been advanced regarding the etiology that all of them cannot be mentioned, but some of the most important are discussed I certainly have no desire to discredit the very excellent work that has been done in pellagra investigations intended to prove that it is entirely a vitamin deficiency disease On the contrary I am thoroughly convinced that food deficiency is the most important cause of pellagra, but I believe that the facts set forth in this book, as gleaned from the observations and studies of many capable clinicians, justify the assumption that in the uncharted seas of the mysterious realms of pellagra there are continents yet to be discovered

Regarding the symptoms, diagnosis, prognosis, and treatment of pellagra, there is no controversy, and on those phases of the disease, essential in its management, I have endeavored to present a practical treatise so that the book may be found helpful to the general practitioner when called upon to diagnose and treat pellagra Prevention is of equal importance to treatment, and the extensive section on "prophylaxis" has been prepared in the hope that public health officials and nurses, and others engaged in the fields of preventive medicine, may find in it information useful in applying methods which eventually will decrease the incidence of pellagra in the United States to the irreducible minimum

SECTION I

HISTORY AND EPIDEMIOLOGY

CHAPTER I

EARLY HISTORY AND EPIDEMIOLOGY OF PELLAGRA

Spain—More than two centuries ago, in 1725, Don Gaspar Casal, physician to Philip V of Spain, recognized among the peasants in the province of Asturia a disease entity different from any malady then known to physicians. The disease was so severe and its ravages so serious that at first he regarded it as atypical leprosy, which he called "scorbutic leprosy." It also was called by the Spaniards "mal de la rosa," "sickness of the rose." Casal's description of pellagra was not published until 1762, three years after his death. All authorities seem to agree that Casal's classical description of the skin lesions and the digestive and nervous manifestations of the disease, which he recognized, was the first reference to pellagra that appeared in medical literature. Aside from Casal's description of pellagra, Spanish physicians appear to have made no other contributions of value to the literature on the subject. The Spaniards believed that pellagra, like syphilis, was brought to Spain by sailors who were said to have contracted it from the American Indians, but there is no evidence to substantiate that assumption.

Italy—Pellagra was next recognized in endemic, or epidemic, form in the Kingdom of Milan, now a part of Italy, and was described by Frapolli in 1771. Pellagra appears to have spread rapidly throughout northern Italy and then to central and southern Italy. Only a few cases have been reported in Rome and its vicinity and it is said that it has never invaded Genoa. The statement has been made that pellagra has not been found on the islands of Sicily, Corsica, and Sardinia, though the natives consume the same variety of foods and their living conditions

are the same as those of their fellow countrymen on the Italian peninsula When pellagra was first discovered in Italy, the mortality was high in numerous epidemics among the peasant population, and judging from the enormous literature on the subject contributed by many Italian pellagrologists, it was Italy's most serious health problem for a century

The late H F Harris, of Atlanta, who wrote the most comprehensive monograph on pellagra that has been published in the English language, impressed by the thoroughness of the investigations of the Italians on all the various phases of pellagra, dedicated his book "to the memory of those two master pellagrologists, *Gaetano Strambio, Sr, and Michael Gheradini*, who devoted the best part of their lives to the study of pellagra" Strambio and Gheradini were two of the many Italian physicians who spent years in the effort to solve the pellagra problem Cesare Lombroso renowned no less for his studies on criminology than for his researches on pellagra, is best known to Americans because of his toxin from spoiled maize theory as the cause of pellagra, but Morelli, Lussana, Frua, Selmi, *Gemma, Sambon, Alessandrini, and a legion of other Italian* physicians have made valuable contributions to the study of pellagra The fact is that much of the early work done on the etiology of pellagra in the United States merely duplicates that which the Italians had carried on from fifty to one hundred years before

Pellagra Now a Rare Disease in Italy—The statistics on pellagra in Italy, published by Claude Lavinder in 1909, showed an amazing, if not incredible, decrease from 1898 to 1907

TOTAL NUMBER OF PELLAGRINS IN ITALY, BY CENSUS

1879	97 855
1881	104 067
1899	72 603
1905	55 029

TOTAL DEATHS FROM PELLAGRA IN ITALY

1898	3,987
1900	3,788
1904	2 363
1906	439
1907	576

In December and January following the end of the World War in November, 1918, I had the privilege of making some investigations regarding food conditions and nutritional diseases in Italy. Having been interested particularly in pellagra, I had hoped to study the disease as it exists among the Italians. To my surprise I could find no pellagra in Italy.

The surgeon general of the Italian Army said that only a few cases had been reported among the five or six millions of soldiers who had been drafted in Italy. The only statistics that could be found on pellagra in Italy then were those among the nearly one million young men who had been drafted into the Italian army in 1918, only 34 had been rejected because of pellagra. The Vital Statistics Division of the Italian Public Health Service was visited, in the hope to secure some data on the morbidity and mortality of pellagra, but the physician in charge said that there were no reliable statistics concerning pellagra in Italy. He said that he was quite sure that pellagra had decreased enormously in the past two decades, but he had no data to prove it. Bastianelli, the great Italian surgeon, said that if pellagra existed in Rome he did not know it, and that in his large surgical experience, probably thirty years, he had never seen a case of pellagra.

It is said that there has been an increase in the prevalence of pellagra in Italy in the last few years and that prior to Italy's entry in the European War, June 10, 1940, Mussolini had undertaken the task of eradicating the disease from among his peasant classes.

France.—Hameau reported that pellagra was endemic, or epidemic, in southwest France in 1828. He believed that pellagra had existed in Gironde, a French province, for at least half a century before that time. Pellagra appears to have spread rapidly over many regions in France, a few cases were reported in Paris, and then it gradually disappeared until by 1890, "mal de Saint Rose" had ceased to exist in France. I served in France for ten months during and immediately after the World War, and though many inquiries were made, no American or French physician could be found who had seen a case of pellagra.

While apparently pellagra has never been a serious problem in France, Roussel's two compilations of the literature on pellagra published in 1845 and in 1866 presented valuable data for use by those interested in the study of pellagra. Later, in 1908, Marie published a book, in which there was little original material, but in which he presented an excellent summary of the knowledge of pellagra that had accumulated up to that time. Since American physicians are more proficient in reading French than Italian, Roussel's and Marie's books had a profound effect in molding the opinion of Southern physicians (to the maize toxin theory of its causation) in the early years of their study of pellagra.

Austria-Hungary and Rumania.—Pellagra appears to have extended from Italy into Austria, but there has been a marked decrease in the severity of the disease and in the number of cases reported in Austria. Neusser, the great Viennese clinician, made a thorough study of pellagra in the Austrian Tyrol and in Rumania. His book, published in 1887, in which he announced his theory that pellagra is due to a toxin, generated by bacterial action in the intestines, and in which he discussed the clinical aspects of the disease, has been one of the classics on pellagra studied by American physicians.

Pellagra must have been an infrequent disease in Austria in 1906, at least in the vicinity of Vienna. In January, 1919, I visited the cities of Trent, Trieste, and Fiume, then a part of Austria Hungary, and was informed that pellagra did not exist in them, but the disease was said to prevail in the "hinterland" of Trieste and Croatia.

Pellagra crossed over the Transylvanian Alps from Austria into Hungary, and extended from there to Rumania where in 1912 it was stated that out of a population of 5,000,000 there were 75,000 pellagrins. Pellagra extended from Rumania to Serbia and Bulgaria and into Poland, southwestern Russia, Bosnia, and Herzegovina, where it is more or less endemic at this time. There seems to be little pellagra in Turkey, and it is said to be a rare disease in Greece.

England, Germany, and Northern Europe.—Sporadic cases, usually associated with alcoholism and secondary to chronic diseases in which undernutrition was a factor, have been re-

ported in England, Ireland, Germany, and the Netherlands, but the disease has not been found to be endemic in the British Isles or in any country in northern Europe, except Scandinavia I made investigations of food conditions and nutritional diseases in Germany in 1919, and though the Germans suffered terribly from the lack of food, particularly milk, eggs, meats, and fats, German physicians stated that pellagra did not exist then, and had never been reported in Germany

Egypt —Pellagra was first reported in Egypt in 1847 by Prumner and described by him as a type of leprosy Pellagra in Egypt, as elsewhere, appears to be largely a rural disease, and it is rare in such cities as Port Said, Suez, and Alexandria Recent information on the prevalence of pellagra in northern Africa seems to indicate at the present time that pellagra is more widespread and more severe in Egypt than in any other country in the world Sabra reports that since the natives consume a large amount of alcoholic beverages in Egyptian cities, pellagra is now an urban as well as a rural problem in Egypt Ellinger, Hassan, and Taha recently (1937) examined 204 natives selected at random in villages of the Nile Delta and found that 34 per cent of them were suffering from pellagra

The Far East —In the last few years sporadic cases of pellagra have been reported in India and China It is more than passing strange that in all the floods and famines in those countries no outbreaks of pellagra have been reported A few cases have been recognized in Japan, the Philippines, Hawaii, and Australia

Mexico and Central America —Pellagra has been known to be endemic in Mexico since 1896 when Noles reported a number of cases in Yucatan Pellagra also exists in other Central American countries and in South America, but no serious outbreaks or epidemics have been reported in the Western Hemisphere, except in Yucatan and in rural or suburban communities in the South

Deeks, in 1912, reported a number of cases of pellagra that occurred among the laborers who were brought from all parts of the world to work on the Panama Canal More recent reports show that pellagra is rare among the Americans residing in the Canal Zone, but that a number of patients have

been treated among native Panamanians in Santo Thomas Hospital in the City of Panama Frayser and Smith reported that 51 patients with pellagra had been admitted to Ancon Hospital, an American hospital for Canal Zone employees, from 1909 to 1915 Nathan Barlow, United Fruit Company physician, stationed in Honduras, said that he and three other physicians had been on the outlook for pellagra for two years They "were unable to find a single case which could possibly, by the wildest stretch of imagination, be considered pellagra"

It is interesting that pellagra prevails more in the southeastern sections of the United States than it does in tropical America In 1924, I was invited to present a paper on pellagra at the International Conference on Health Problems in Tropical America held in Kingston, Jamaica I also visited the United Fruit Company hospitals, usually containing about two hundred beds each, in Honduras, Guatemala, and Costa Rica Malaria and dysentery were the prevailing diseases, but not a case of pellagra was seen in any one of those hospitals

In the city hospital of Guatemala City, in addition to malaria and dysentery, there were many cases of tropical leg ulcers, and various types of filarial disease, but no pellagra In the hospitals of Cuba, the Canal Zone, and Panama, malaria and dysentery were among the prevailing diseases but there was no pellagra Syphilis, frequently found in pellagrins, is almost universal among the poor and ignorant classes, representing a large proportion of the population in the West Indies and the Central American countries

While the food factor in pellagra will be discussed in another section, it is relevant to mention that a high carbohydrate, very low protein, and vitamin deficient diet is the rule in the Central American republics, among the most degenerate and most poverty stricken people in the Western Hemisphere Likewise most of the few and far between prosperous families in the Islands of the West Indies and in Central American countries live on a diet deficient in vitamins and proteins One wonders why pellagra is not as epidemic in those countries as it is in some of the rural districts of the Southern states?

CHAPTER II

HISTORY AND EPIDEMIOLOGY OF PELLAGRA IN THE UNITED STATES

Gray, of Utica, New York, reported the first case of pellagra in the United States in 1864 Tyler, of Summerville, Massachusetts, reported another case in 1864 Sherwell, of Brooklyn, in 1883, reported a case in an Italian sailor, and he reported a second case in 1902 Bemiss, of New Orleans, diagnosed a case of pellagra in 1889, and in the same year Mask, Bellamy, and Wood, of Wilmington North Carolina, each reported cases in which the diagnosis of pellagra was suspected H F Harris, of Atlanta, in 1902, reported a case of uncinariasis in an individual presenting typical symptoms of pellagra

Early in 1905 George Searcy, then in charge of the Alabama State Hospital for Insane Negroes at Mount Vernon, observed a new type of a very fatal disease which had appeared among the inmates of that institution, but it was not until 1906 that he made the diagnosis of pellagra Searcy's description of the alimentary tract symptoms, the skin lesions, and the nervous and mental manifestations of pellagra will remain as one of the classics in medical literature E L McCafferty, who became Superintendent of the Alabama Insane Hospital for Negroes in 1906, in 1908 reported in detail the cases which occurred in the Mount Vernon Hospital from 1906 up to that time

Following the report of the Alabama cases, similar outbreaks were reported by Babcock in the Insane Hospital in South Carolina and by the physicians in charge of the Illinois Insane Hospital In a few months the disease was found to be endemic, or epidemic, in Alabama, Mississippi, Louisiana, Texas, Georgia, North Carolina, South Carolina, Kentucky, Tennessee, and to a less extent in Florida, Virginia, Arkansas, and Oklahoma In a few years sporadic cases of pellagra had been reported in most of the Eastern, Northern, North Central, and Western States

Pellagra a National Problem—Pellagra is today a national problem Vital statistics from the United States Bureau of

the Census, with every state in the Union in the Registration Area, and which are approximately 90 per cent accurate, showed that in the year 1936, 3,740 persons died from pellagra. In 1929 when the peak of mortality from pellagra apparently was reached, the U. S. Census Bureau reported 6,793 deaths from pellagra. The state of Texas was not in the registration area at that time, and adding 1,000 deaths from pellagra in 1929, a low estimate, the total deaths in the United States from pellagra in 1929 numbered approximately 7,793. Thus it will be seen that in eight years there was at least a 50 per cent reduction in the death rate from pellagra in the United States.

Decrease in the South from 1929 to 1936.—The decrease in the number of deaths from pellagra was reduced from 7,358 in 1929 to 3,401 in 1936 in the 13 southeastern states while in the remaining 35 states there was an increase in the number of deaths from pellagra from 265 in 1929 to 339 in 1936.

Table I shows the decrease in pellagra in 13 states in the southeastern section of the United States.

TABLE I

	1929	*1936*
Alabama	666	507
Arkansas	515	213
Florida	315	133
Georgia	878	387
Kentucky	133	88
Louisiana	285	116
Mississippi	754	269
North Carolina	950	351
Oklahoma	279	175
South Carolina	945	275
Tennessee	412	243
Texas	1000*	714
Virginia	228	130
Totals for 13 states	7 358	3 401

*Estimated number

Table II shows the number of deaths from pellagra in the remaining 35 states and the District of Columbia.

Increase in Pellagra in Northern and Western States.—It is interesting to note that California with 87 deaths, New Mexico with 47 deaths, and Missouri with 27 deaths in 1936, with climate approaching that of Kentucky, Arkansas, Oklahoma and Texas, had a larger number of deaths from pellagra than

TABLE II

	1929	1936
Arizona	8	5
California	42	87
Colorado	4	5
Connecticut	4	6
Delaware (1)	0	0
District of Columbia	2	3
Idaho	0	1
Kansas	9	13
Maine	3	1
Maryland	10	8
Massachusetts	11	15
Michigan	8	6
Minnesota	5	2
Missouri	27	37
Montana	1	1
Nebraska	3	1
Nevada	2	0
New Hampshire	1	1
New Jersey	2	8
New Mexico	31	21
New York	23	27
North Dakota	0	0
Ohio	21	26
Oregon	3	2
Pennsylvania	16	12
Rhode Island	2	1
South Dakota	0	1
Utah	0	0
Vermont	1	0
Washington	0	5
West Virginia	5	10
Wisconsin	2	3
Wyoming	0	0
Total for 35 states	265	339

Massachusetts (15 deaths), Wisconsin (3), and Washington (5), in 1936, states in which climate is colder Can it be said that pellagra is spreading westward and to a less extent into the Eastern, North Central, and Western states? California with 87 deaths from pellagra in 1936 lacked only one of having as many deaths from that disease as Kentucky in which 88 deaths were reported

Blankenhorn, of Cincinnati, is of the opinion that there are many unrecognized cases of pellagra in the states in which only a few deaths a year are reported at this time, and that as physicians become more familiar with the disease they will diagnose more cases Fisher, of Youngstown, Ohio, in a paper on "Pellagra in the North," in 1928, said that in his opinion there are many more cases of pellagra than are reported, for the

reason that the diagnosis is not made by physicians who are under the impression that pellagra is a rare disease outside of the South

In the Southern states until physicians became "pellagra conscious," they failed to diagnose many cases of pellagra, but now it is probable that in the South physicians err in diagnosing many cases as pellagra which should not be so diagnosed Certainly at this time I am having more cases of pellagraphobia, and more cases that have been diagnosed incorrectly as pellagra than I am having of real pellagra It is a fact that many cases of chronic nephritis and other fatal diseases in which the patient has a red tongue, stomatitis, and diarrhea, with delirium, and death, are *diagnosed* as pellagra, and *in the South, a not in* considerable proportion of the patients with acute psychoses and toxic delirium, with and without diarrhea and dermatitis, are misdiagnosed as pellagra It therefore seems probable that in the South physicians err in making the diagnosis of pellagra too frequently

Statistics for 1938—The last available statistics reported by the National Bureau of Statistics show that in the year 1938 there were 535 fewer deaths from pellagra in the United States than in the year 1936, a reduction of 7 per cent (Table III) With the application of nicotinic acid and liver therapy, the pellagra death rate may be expected to make further drops, and with continued improvement in nutrition and in the sanitary conditions in the rural districts in the states showing the highest incidence of pellagra, there will be a marked reduction in the total number of cases The pellagra problem is far from being solved, but no longer may it be regarded as one of the major public health problems in any state in the Union

Why Is Pellagra Less Prevalent in Virginia, Maryland, and Pennsylvania Than in North Carolina, South Carolina, and Georgia?—It is interesting to note the difference in the number of deaths from pellagra in Virginia, Maryland, and Pennsylvania in the north, and North Carolina, South Carolina, and Georgia in the south These states have been in the registration area for many years, and their vital statistics must be regarded as at least 90 per cent accurate Table IV gives the number of recorded deaths from pellagra and malaria in Penn

TABLE III

DEATHS AND DEATH RATES (PER 100,000 ESTIMATED POPULATION) FROM PELLAGRA UNITED STATES, 1938

AREA	NUMBER	RATE
United States	3,205	2 5
Alabama	349	12 1
Arizona	4	1 0
Arkansas	181	8 8
California	66	1 1
Colorado	1	0 1
Connecticut	2	0 1
Delaware	1	0 4
District of Columbia	4	0 6
Florida	105	6 3
Georgia	365	11 8
Idaho	–	–
Illinois	14	0 2
Indiana	4	0 1
Iowa	1	*
Kansas	5	0 3
Kentucky	64	2 2
Louisiana	148	6 9
Maine	2	0 2
Maryland	7	0 4
Massachusetts	11	0 2
Michigan	7	0 1
Minnesota	3	0 1
Mississippi	267	13 2
Missouri	22	0 6
Montana	–	–
Nebraska	2	0 1
Nevada	–	–
New Hampshire	–	–
New Jersey	11	0 3
New Mexico	17	4 0
New York	26	0 2
North Carolina	254	7 3
North Dakota	1	0 1
Ohio	13	0 2
Oklahoma	119	4 7
Oregon	1	0 1
Pennsylvania	11	0 1
Rhode Island	1	0 1
South Carolina	234	12 5
South Dakota	–	–
Tennessee	210	7 3
Texas	544	8 8
Utah	–	–
Vermont	–	–
Virginia	114	4 2
Washington	1	0 1
West Virginia	7	0 4
Wisconsin	6	0 2
Wyoming	–	–

*Less than one tenth of 1 per 100 000 estimated population

Note *Rates based on 1937 estimated population no estimates made for 1938*

sylvania, Maryland, Virginia, North Carolina, South Carolina, and Georgia It also is interesting to compare the number of deaths from pellagra with those from malaria in the states extending from Pennsylvania to Georgia

TABLE IV

		PENNSYLVANIA	MARYLAND	VIRGINIA	NORTH CAROLINA	SOUTH CAROLINA	GEORGIA
1936	Pellagra	12	1	130	351	275	387
	Malaria	8	1	17	150	435	61[illegible]
1935	Pellagra	15	4	140	385	298	367
	Malaria	5	3	16	91	430	381
1934	Pellagra	15	4	125	438	343	349
	Malaria	4	1	10	66	354	410
1933	Pellagra	12	4	118	392	328	417
	Malaria	4	2	10	51	244	367
1932	Pellagra	11	5	128	479	434	495
	Malaria	10	1	6	53	234	315

These statistics seem to show that the climatic conditions which are favorable to the production of malaria may account in part at least for the low incidence of pellagra in the states north of Virginia There is no relationship between malaria and pellagra except that malaria may be a predisposing cause, but it seems more than a coincidence that both diseases prevail in warm climates

It will be seen that in the year 1936 pellagra claimed 12 victims in Pennsylvania, 1 in Maryland, 130 in Virginia, 351 in North Carolina, 275 in South Carolina, and 387 in Georgia Why should pellagra prevail to such an extent in Georgia, South Carolina, and North Carolina and become less prevalent in Virginia and Maryland and almost to the vanishing point in the populous state of Pennsylvania?

Beall, of Fort Worth, Texas, observed that in El Paso County in the Panhandle of Texas, in which the altitude produces a colder climate than in Central Texas, there was little or no pellagra, while in the rural districts of the lowlands of Texas it was a major health problem He called attention to the fact that when pellagrins are sent to colder climates, and in the winter, they improve rapidly What is there about altitude and low temperature that are inimical to pellagra? Pellagra prevails most in the same localities in which malaria, hookworm, and amebiasis are health problems Why?

Is all the poverty in the United States in the South Atlantic and Gulf States? Are there no poverty and malnutrition in Maryland, Pennsylvania, and New York? Government statistics show that about one in every five persons are on relief in Pennsylvania and New York, while in Alabama and other Southern states only about one in ten persons are being helped by the government Why is there so little pellagra in states with so large a proportion of indigents?

Otto F Geck, who came down to Virginia from New York to solve the health problems of the South, working in a Virginia State Hospital for Insane Negroes (2,400 inmates) in 1930, found 4 male pellagrins per 1,000, and between 45 and 50 female pellagrins per 1,000, a ratio of 10 females to 1 male The Thompson Pellagra Commission found a ratio of 2½ females to 1 of male pellagrins Geck observed negro men chewing tobacco intensively, while fewer women "chewed" This fact suggested to him that chewing tobacco might contain some protective quality, possibly the pellagra preventive vitamin, the pellagra preventive factor now known to be nicotinic acid Geck suggested experiments to determine whether or not chewing tobacco will prevent and cure pellagra As yet, Geck's theory that Virginia tobacco may be rich in the pellagra preventive factor has not been tested, or at least no report of such researches has appeared in the literature

Can it be that North Carolina tobacco, rich in nicotine, is deficient in nicotinic acid, while the weed in Virginia is rich in the pellagra preventive factor? If so, that might explain the difference in the number of deaths from pellagra in the two states It is more than passing strange that Virginia cigarette manufacturers have not learned of the pellagra-preventive factors in Virginia tobacco but in the near future billboard and newspaper cigarette advertisements may read "Reach for a Virginia cigarette and get a lift from nicotinic acid" It may be that the reason the men and women in Maryland and Pennsylvania have so little pellagra is that they chew Virginia tobacco which is rich in the pellagra preventive factor and scorn the North Carolina product which is poor in nicotinic acid while the tobacco chewers in South Carolina and Georgia

masticate the "Old North State" plug, which is loaded with nicotine, but deficient in nicotinic acid

It should be added seriously that Spies called attention to the fact that nicotine and nicotinic acid are very different chemicals, having entirely different properties, and there is no evidence to support Geck's suggestion that tobacco protects against pellagra

I believe that the reason for the low incidence of pellagra in Pennsylvania, Maryland, and Virginia is that the inhabitants of those states eat very little western ground corn meal, while in North Carolina, South Carolina, and Georgia, devitaminized, white corn meal bread is the principal article of food among the poor I do not intend to revive the corn toxin theory as the sole cause of pellagra, though it may be a predisposing factor in some cases, but I do insist that the most important problem in the prevention of endemic pellagra in the South is for the inhabitants of the rural districts to be taught to substitute bread made from whole wheat, rye, and barley, and home raised, home ground, whole grain corn meal for western ground devitaminized white corn meal It also may be a fact that the indigent among the Virginians, Marylanders and Pennsylvanians eat more meat and vegetables and less white corn meal bread and syrup than do the poorer classes in North Carolina, South Carolina and Georgia

How Long Has Endemic Pellagra Existed in the United States?—The question of how long pellagra has existed in the United States was discussed at many medical meetings after the outbreak at Mount Vernon was reported in 1906 Babcock stated that in studying the records of the South Carolina Insane Hospital he found evidence that it had existed in South Carolina since 1884 Kern, of Corsicana, Texas, a Confederate surgeon, thought it possible that pellagra prevailed among the Union soldiers who were in the Andersonville prison during the Civil War, but others believe that typhoid fever and amebic dysentery were responsible for the heavy death rate among soldiers both in Federal and Confederate prisons Bass, of New Orleans, reported cases of patients with histories of having had symptoms of pellagra for a number of years before the disease was recognized

On the other hand, Eugene Bondurant of Mobile, formerly Professor of Neuropsychiatry in the University of Alabama and a neuropsychiatrist of large experience, with pathologic training in the University of Vienna, stated that he had performed more than 1,000 autopsies on patients who died in the Alabama Insane Hospitals, and he had never found a case which resembled the pellagra he had seen at Mount Vernon

I find it difficult to believe that pellagra could have been endemic in the South prior to 1906, though no doubt there were occasional cases of secondary and alcoholic pellagra

Pellagra Commissions and Conferences—In less than two years after pellagra was found to be endemic in Alabama, well qualified physicians were employed in a number of states to devote all of their time to studying the disease and to reporting methods for preventing the dreaded pellagra Among the Pellagra Commissions who studied the disease in the late nineties were those from the states of North Carolina, South Carolina, Tennessee, and Illinois

South Carolina became the center of pellagra studies in the late nineties Babcock and Watson, who in 1907 found a number of cases in the South Carolina State Hospital for the Insane, called a Pellagra Conference to assemble in Columbia, South Carolina, in 1908 Physicians from all over the South were present and carried back to their home states much information regarding the new disease In 1912 under the leadership of J W Babcock, a National Pellagra Conference was called and was widely attended The publication of the transactions of these two Pellagra Conferences provided much needed material to the medical profession for study in diagnosing and treating the disease

Philanthropy was called upon, and a Mr Thompson, of New York, provided the money for a survey and a study of the epidemiology of pellagra in the cotton mill districts in the vicinity of Spartanburg, South Carolina The Thompson Pellagra Commission's report will be discussed under the infections theories It made a profound impression upon the medical profession at the time, and convinced many physicians who had experience in dealing with pellagra that soil pollution is the source of the disease in the South

Of lesser importance, but highly instructive to those who attended and to those who read the proceedings published in the *Gulf States Journal of Medicine and Surgery* (Mobile), December, 1908, was the Gulfport Pellagra Conference held under the auspices of the Harrison County, Mississippi, Medical Society. A large number of physicians who had experience with pellagra from the states of Mississippi, Louisiana, and Alabama participated in the Gulfport Pellagra Conference.

The United States Public Health Service and Pellagra.—When pellagra was found to be a serious endemic disease in various Southern states, health officials appealed to Surgeon General Wyman of the United States Health Service for aid in combating its ravages. Dr. Claude Lavinder was detailed to study the disease and for several years he devoted his entire time, working with the state and local health authorities in studying pellagra from every angle and in disseminating information regarding the known facts of the disease among physicians in localities in which cases had been reported. He and the late Colonel Jos. F. Siler and Colonel H. J. Nichols, of the United States Army, reviewed the foreign literature on pellagra and prepared a booklet, giving the essential information regarding the history, epidemiology, symptomatology, prevention, and treatment of the new and terrible disease that had appeared in many rural and suburban communities in the South. When the history of pellagra in the United States is written, the name of Claude Lavinder should be found high among the pioneer physicians who served their country faithfully and efficiently in fighting the ravages of a disease of unknown origin.

Surgeon Generals Rupert Blue, a South Carolinian, and Hugh Cummings, a Virginian, of the United States Public Health Service during their administrations, gave every possible aid to health officials in the states affected in the study and prevention of pellagra. Though pellagra is not now an acute problem, Surgeon General Thomas Parran has continued to aid the states in their efforts to eradicate the disease.

The United States Public Health Service provided Joseph Goldberger with capable associates who themselves have made valuable contributions to the study of pellagra. Wheeler and Voegtlin were associated with Goldberger in the early years

of his work, and later Sebrell, all of whom have contributed meritorious studies on the food factor in pellagra Goldberger and his associates in their experiments proved that vitamin B has a pellagra-preventive (P P) factor in addition to its anti neuritic (anti beriberi) qualities

There can be no question but that the United States Public Health Service has lived up to its opportunity by rendering greatly needed help to the state and local health agencies in their efforts to control the ravages of pellagra Lavinder, Goldberger, Wheeler, and Sebrell also have rendered service of inestimable value to individual physicians in communities in which outbreaks, or epidemics of pellagra have occurred

Our Debt to State Public Health Officials —It should be remembered also that during the last thirty years there has been an unprecedented development of the health departments in all the states in which pellagra is endemic, and that while the morbidity rates from pellagra have been reduced by 60 or 70 per cent in the last thirty years, there has been an almost parallel decrease in the number of deaths and the number of cases of malaria, uncinariasis, typhoid fever, amebic dysentery, and other diseases It also is significant that pellagra, malaria, typhoid fever, uncinariasis, and amebic dysentery have become milder diseases, and the malignant types of those diseases which were seen frequently thirty years ago have been observed rarely in the last few years

The gratitude of the Nation and of the South, in particular, is due the underpaid public health officials in the state health departments and the county health units in the states in which pellagra has been endemic and epidemic for the last thirty four years, for their part in reducing the incidence and the death rates of pellagra, malaria, uncinariasis, typhoid fever, amebic dysentery, and other diseases There are tens of thousands of men, women, and children enjoying health and prosperity to day, who would have been in their graves had it not been for the vision and the labors of specialists in preventable diseases who are devoting their lives to making our country a better and safer place in which to live

The Philanthropy of John D Rockefeller and the Service of Charles Wardell Styles —In expressing gratitude to those to

whom it is due for their part in improving health conditions in the South, the philanthropy of John D Rockefeller, and the indefatigable efforts of Dr Charles Wardell Styles, of the United States Public Health Service, should not be forgotten The five million dollars given by Mr Rockefeller to eradicate hookworm in the South not only did much toward curing and preventing uncinariasis, but it aroused public sentiment in the South to a realization of its health needs, and to an appreciation of the opportunity to eradicate all the tropical diseases which had interfered with its agricultural and industrial development The origin of the development of the public health agencies that are now the pride of the South can be traced to a considerable extent to the vision of Dr Charles Wardell Styles and to the philanthropy of John D Rockefeller It was fortunate for the South and the Nation that, when pellagra became endemic and epidemic in the United States, through the munificence of John D Rockefeller, a great humanitarian, public health agencies which could cope with that, or any other, disease which might appear were being developed in all the states affected

It should be added that the philanthropy of John D Rockefeller for the prevention of disease in the South did not end with the five million dollar hookworm campaign, through the International Health Board, the Rockefeller Foundation has contributed many more millions to supplement the needs of the state departments of health in the various Southern states John H Ferrell, trained in public health work in North Carolina and familiar with the health problems of the entire South, has seen to it that the Rockefeller funds expended in the South were placed where they would do the most good

The Country Doctor and Pellagra—When it became known that pellagra was endemic and epidemic in the South, the progressive physicians in all the Southern states became intensely interested in the new disease They lost no time in informing themselves on all phases of the disease, particularly its prevention and cure No army ever went into battle with greater zeal, courage, and patriotism than did the physicians of the South when they prepared themselves for the attack on pellagra Each individual physician was a medical official in the war

of his work, and later Sebrell, all of whom have contributed meritorious studies on the food factor in pellagra Goldberger and his associates in their experiments proved that vitamin B has a pellagra preventive (P P) factor in addition to its anti neuritic (anti beriberi) qualities

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against a disease which threatened to become a scourge to the South, and some of the most constructive work on pellagra was accomplished by rural physicians

The country doctors in the South in the early days of pellagra proved themselves the equals of the clinicians in the medical centers, and in reading the literature on pellagra, one is impressed by the many excellent articles by physicians in localities, sometimes far removed from cities, and even miles from railroads Many of the papers on pellagra by country doctors, in which they outlined their experiences in diagnosing and treating the disease and recorded their observations regarding the habits and environment of the pellagrins under their care, are today among the most valuable contributions to the literature on pellagra It is with regret that space cannot be given to mention the names of all those who merit recognition for distinguished service in the war that has been waged on pellagra for the last three decades

The physicians of the South, including those who are devoting their lives to the prevention of disease quietly and without ostentation, have worked from day to day and from year to year to cure and prevent the diseases that are endemic and epidemic in a balmy, equable climate, and they deserve ninety five hundredths of the credit for reducing the death rates from pellagra by at least 75 per cent in the last thirty years They have worked without praise or publicity, but the "travail of their souls has been satisfied" with the knowledge of "work well done," which after all, is the greatest reward that can come to those who serve mankind

CHAPTER III

ALCOHOLIC PELLAGRA

The increase of alcoholic pellagra in cities, and in regions of the United States in which pellagra formerly was a rare disease, seems to indicate that ethyl alcohol, the end product of the fermentation of corn, rye, sugar, and other carbohydrates, is one of the toxins which may be factors in the etiology of pellagra While not the only etiologic factor, ethyl alcohol, a toxin, described by Dorland s *American Medical Dictionary* as "a narcotic poison it used in large doses," certainly is the underlying, or primary cause of alcoholic pellagra Because ethyl alcohol, a known toxin, is a factor in many cases of pellagra, it may be discussed as the simplest example of the toxins as related to the production of pellagra

When pellagra became endemic in the Southern states, it was observed that chronic alcoholics were very susceptible to the disease The spoiled maize theory was generally accepted at that time, and it was thought that corn whiskey contained the toxin responsible for pellagra in alcoholics Subsequently cases of pellagra were reported in sections of the country in which rye whiskey was the popular toxic narcotic, and later it was recognized that those who drank excessively of beverages of any kind, containing ethyl alcohol, became potential victims of pellagra A large proportion of the cases of pellagra reported from the eastern, northern, and western cities in recent years have been in chronic alcoholics

Reported Cases of Alcoholic Pellagra in the North and East — Klauder and Winkelman, in 1928, in reviewing the histories of 100 pellagrins in the Philadelphia General Hospital, found that "alcoholism runs like a red streak" through nearly all pellagra patients Only three of the 100 patients did not give a history of alcoholism Y C Shattuck, in Boston, reported 144 cases of pellagra, 78 per cent of the patients gave histories of the excessive use of alcohol

Howard Fox reported 37 cases in Bellevue Hospital in New York City from 1914 to 1928, 20 patients gave histories of alcoholism, 15 "were heavy drinkers of whiskey or gin," while 6 were "moderate drinkers of alcohol"

Spies and Blankenhorn reported a series of 200 patients in Cleveland, Ohio, suffering from chronic alcoholism and pellagra They were impressed with the fact that "pellagra in the northern part of the United States is for the most part associated with chronic alcoholism while that found in the Southern states is not" They concluded, however, that pellagra whether endemic, or of alcoholic origin, is essentially the same disease Spies and J B McLester cleared up the symptoms of pellagra in alcoholics by the use of yeast, and later by nicotinic acid They showed that in Birmingham alcoholic pellagra is the same disease as the endemic type

Busman, of Pittsburgh, in reporting 27 cases of pellagra observed by him over a period of ten years, said "We are encountering frequent cases of pellagra in the North, some of which occur in individuals on normally balanced diets" There was a history of alcoholism in 10 of Busman's 27 cases Ten gave no history of abnormal or deficient diet Only 5 were definitely emaciated as a result of chronic malnutrition

Guthrie studied 14 patients with pellagra admitted to the Boston Psychopathic Hospital Six of the 14 patients were profoundly alcoholic For comparison, 6 cases of alcoholic psychoses in nonpellagrins were studied These 6 "showed signs of dietary deficiency differing only in degree from the group of 14 pellagrins" In other words, 6 alcoholic psychotic patients, who did not develop pellagra, had about the same dietary history as the 14 who developed the disease

Guthrie in discussing the relation of alcoholism to pellagra said

> "It is known that alcohol may seriously influence absorption and assimilation Whether the pellagrous symptoms in chronic alcoholics are due to malabsorption, or to decrease in the total intake of vitamins, or to both, is an interesting problem The gastric secretions are influenced quite similarly in chronic alcoholism and pellagra, i e, the secretion of hydrochloric acid is diminished or absent This fact has been emphasized by those who believe pellagra to be an infectious disease, because, they claim, the alimentary tract has lost its natural protection against invasion by pathogenic micro organisms The loss

of appetite with decrease in the total intake of food in chronic alcoholics is a more simple and logical explanation for the cause of pellagrous symptoms which are not infrequently associated with chronic alcoholism."

Sweitzer, of Minneapolis, reported that 7 of the 8 patients with pellagra whom "he had seen had been on protracted sprees for weeks and months." One of his patients "was a fat prosperous man of fifty five, living in the country. He came in very drunk and said that he had drunk all his life."

Boggs and Padget in an analysis of 102 cases of pellagra treated in Baltimore found "40 cases, definitely based on alcoholism in that the condition developed toward the end of a prolonged debauch, or occasionally in individuals accustomed to a heavy intake of distilled liquors. Of the 40 cases in which the history of alcohol was definite and clear cut, in 36 there was the story of a spree, which had lasted for some four to six weeks. Most of these patients were admitted either still intoxicated, or showing definite postalcoholic manifestations. The remaining 4 had not been on a spree, but for long periods had been accustomed to a large daily intake of distilled liquors."

That pellagra is one of the manifestations of terminal disease in alcoholics is shown by the fact that in Boggs and Padget's 102 cases, 45 per cent showed involvement of the spinal cord. Fifty one patients, 50 per cent, had some type of psychoses, but of these, only 26 (25.5 per cent) were thought to be pellagrous in their origin. Fourteen had typical alcoholic psychoses, such as delirium tremens or Korsakoff's syndrome.

Alcoholic Pellagra in California.—Hein and Merrill in a study of 29 cases in the University of California Service of the San Francisco Hospital, found that

"Alcohol excess was common and apparently often a precipitating factor. Seventeen of the men and 10 of the women gave a history of excessive use of alcohol. One man stated that he used it moderately but went on occasional sprees. The rule was that illness followed sprees at a time when alcohol formed the chief article of food although alcohol may have been acting on the intestinal tract or whole body over a prolonged period."

Charles Edward Smith of Stanford University and Ida May Stevens of the California State Department of Health, in an analysis of 520 cases of pellagra reported in California from

1928 to 1935, found that "217, or 42 per cent, of the 520 patients had a history of alcoholism Persons giving a history of moderate alcoholism, or who were specified as consuming less than an equivalent of 100 c c of alcohol (half a pint of whiskey or a quart of wine) a day, were not included " Of the 217 alcoholics, 148 (62 per cent) were males and 69 (35 4 per cent) were females

In further discussing the relation of alcohol to pellagra in California, Smith and Stevens said

"Excluding the unknown classification, there were 433 cases Half of these cases (50 1 per cent) fell in the alcoholic group, 26 8 per cent *in the dietary deficiency*, 15 9 per cent in the negative group Spies and DeWolf reported that over 90 per cent of their Cleveland pellagrins were alcoholic Notable is the fact that while 62 per cent of the male pellagrins were alcoholic, only 35 per cent of the females were alcoholic The proportion of pellagrins in dietary and illness groups was correspondingly greater among females than males

"Where alcoholism was associated, there were over 200 males per 100 females Aanon mentions that in the Italian alcoholic pellagrins the number of males exceeds the females, contrary to the usual distribution The report of Klauder and Winkelman on alcoholic pellagra in Philadelphia gives a ratio of nearly 250 males per 100 females with antecedent illness and 61 males per 100 females in the unknown groups The excess of females over males in all nonalcoholic pellagrins of California is similar to the sex distribution of endemic pellagra "

Smith and Stevens conclude that "alcoholism plays a dominant role in California pellagra "

Estimated Number of Alcoholic Pellagrins—It is evident from the studies of Smith and Stevens that pellagra is becoming a public health problem of importance in California "In 1935 there were 92 pellagra deaths reported, whereas only 80 typhoid deaths were recorded " Goldberger estimated that there are 20 cases of pellagra to each death reported According to this estimate it is probable that there were approximately 1,840 cases of pellagra in California in 1935 Since pellagra is a chronic disease, often lasting for years, and since many cases are unrecognized in states in which the disease is not considered endemic, it is probable that an estimate of 1,840 cases of pellagra is too low Considering these facts an estimate of 1,000 new cases of alcoholic pellagra a year in California is not too high Since California had a population of 6,829,888 in 1935, about *one eighteenth of the total population of the*

United States, and assuming that the inhabitants of other states consume as much alcohol per capita as in California, an estimate of 18,000 new cases of alcoholic pellagra annually in the United States would not be excessive It is probable, however, that the per capita consumption of alcohol is greater in California, New York, and Illinois and other states with large urban populations, particularly of foreign descent, than in the rural states Of course, it is a pure guess, as are all estimates of the number of cases of pellagra anywhere, but it is probable that there are 20,000 cases of alcoholic pellagra in the United States today, most of which are unrecognized

Alcoholic pellagra is rarely cured except in almshouses, because the victims, in a great majority of cases, as soon as they get out of the hospital will resume the use of the toxic narcotic beverage that caused their malady

Alcoholic pellagra is not a rare disease, and it is increasing directly in proportion to the increased consumption of alcoholic beverages Government reports show that the consumption of beer (5 to 10 per cent), ethyl alcohol, wine (10 to 20 per cent) and whiskey (40 to 50 per cent) has increased from 300 to 400 per cent in the last five years Reports from New York Boston Chicago, and all over the nation show about the same percentage of increase in insanity and cirrhosis of the liver caused by alcohol Haven Emerson, Professor of Preventive Medicine in Columbia University, informed me that in the year 1939 of the 25,000 psychotics admitted to the psychiatric wards of the Bellevue Hospital in New York City, 12,500 were of alcoholic origin It is probable that many of the alcoholic insane also have unrecognized pellagra State and private hospitals all over the United States report that they cannot take care of the psychotic alcoholics they are called upon to treat There can be no question but that there is a similar increase in the number of cases of alcoholic pellagra

Ethyl alcohol is one known cause of pellagra that could be eliminated if all the people of the United States had the good sense and moral courage to abstain from the beverages that contain a toxic, habit forming, narcotic drug

Alcoholic Pellagra in Europe —H F Harris, of Atlanta, who made a thorough study of pellagra in Italy, believed that most

of the cases of pellagra ascribed to alcoholism were not true pellagra but should be classed as parapellagra, but he admits that the excessive use of alcohol may be a factor in bringing on the skin lesions in those predisposed to pellagra He said

'It is commonly believed by competent pellagrologists that the long continued use of alcohol sometimes leads to the occurrence of lesions of the hands and occasionally of the face which somewhat resemble those of pellagra In recent years, Leudet and Bas have reported cases in France, and in Italy Fiorani has recorded a case where a man, who was a drinker, presented all the classic symptoms of pellagra—even showing the blood picture Aanon has recently given some statistics on the subject, and records that of 676 pellagrins in Italy 57 7 per cent were intemperate He says where much alcohol is drunk the men with pellagra exceed the women in number As to whether or not however such a result be possible from the effects of alcohol alone there is some dispute, it being held, for example, by Mark that alcohol (ethyl) alone is incapable of producing pellagroid skin lesions As bearing in the other direction it may be mentioned that Lombroso believes that most, if not all, of the cases of pellagra in Spain a half century ago were of alcoholic origin, an opinion fully concurred in by Calmarza, who is the foremost modern writer on this subject in that country Sanz has also adopted this view On the other hand it seems highly probable that alcohol, owing to its unquestioned deleterious action on the tissues may not unlikely bring into being any latent tendency to skin lesions that may have previously existed—particularly in those who are debilitated *Thus it would seem that the excessive use of alcohol not unlikely* materially augments the tendency to skin eruptions which we know are not uncommon in the badly nourished, and, as Lombroso points out, misery itself is likely to be increased under such circumstances by the subject buying alcoholic drinks instead of food with the little money that comes into his hands Similarly it seems highly probable that the excessive use of wine not unlikely conduces the early development of genuine pellagraderms, and we know from the investigation of Daneo and others that the victims of this malady, with their lowered vitality and abnormal nervous state, frequently become subjects of the alcoholic habit In like manner also the deleterious action of alcohol on the tissues, materially aids in bringing out skin lesions in the earliest stages of the insanities, in paralytics and in those who have developed sclerotic changes in their central nervous systems "

Alcoholic Pellagra in the South—Only 38 (8 8 per *cent*) of Sydenstricker and Armstrong's 440 pellagra patients in the University at Augusta, Georgia, were alcoholics, and they believed that in none of them "did the alcohol have a direct bearing on the development of the pellagra" Alcoholic pellagra must be relatively uncommon in the South I can recall having seen only two cases of alcoholic pellagra, and

I prescribed for each of these patients only one time One was a Confederate general, who lived on his plantation, and "drank mint juleps and straight whiskey like a gentleman"—and he was an educated, cultured gentleman though ignorant regarding the toxic effects of alcohol He died about the year 1912 The other alcoholic pellagrin was a locomotive engineer, who worked for good wages, he was a "good liver" and a "good fellow," who drank "good whiskey" He lost his job on account of his drinking and died in 1910 or 1911 It does not seem likely that avitaminosis could have been the primary factor in the production of pellagra in these two cases

Thatcher, of Little Rock, Arkansas, questioned the diagnosis of pellagra in alcoholics reported in Northern cities He said

> "Several articles have appeared in the literature during the last few years concerning the relationship of alcohol and pellagra One of the last articles was by Guthrie in 1929 He reported on the pellagrins admitted to the Boston Psychopathic Hospital from 1922 to 1928 This study has in it the fallacy that the others have had Only a few pellagrins were studied and conclusions could not be drawn on a small number Those of us who have had experience with chronic alcoholism clinically or at autopsy know that hundreds of such cases occur without any symptoms of pellagra Those of us who have seen many pellagrins know that these people as a rule are not alcoholic"

Thatcher brought up the question of why among the millions of alcohol addicts in the United States there are so few cases of pellagra? The same question may be asked regarding Laennec's cirrhosis of the liver, which by the way, according to Elliott of Chicago, increased 500 per cent in the Cook County Hospital in ten years from 1927 to 1937 Why do only a relatively small number among millions of alcoholics in the United States develop cirrhosis of the liver? France consumes more ethyl alcohol per capita than any other nation in the world, Germany is next in alcoholic consumption, and Great Britain is third Why is there so little alcoholic pellagra in those countries? Cirrhosis of the liver is much more frequent in European countries than in the United States, which may be accounted for by the larger per capita consumption of alcohol in those countries

Liver pathology is almost a constant finding in both endemic and alcoholic pellagra, as it is in Laennec's cirrhosis Can it

be that damage to the liver from alcohol is the underlying cause of the avitaminosis found in alcoholic pellagra?

Cause and Effect—Winston Rutledge, a dermatologist in Louisville, Kentucky, the land of "good old Bourbon whiskey," reported 20 cases of pellagra in chronic alcoholics All of them presented the characteristic skin lesions, with varying degrees of gastrointestinal and neurologic manifestations Five of the 20 alcoholic pellagrins died No report of autopsy findings was made The 15 who recovered improved slowly That the alcohol was the primary cause of the pellagra is shown by Rutledge He said "One patient apparently on the road to recovery who drank a half pint of an inferior grade of an alcoholic beverage had an acute exacerbation of the skin lesions on the backs of his hands"

Spearman and Smith reported pellagra in a 36 year old alcoholic The symptoms, including the skin lesions, disappeared after abstinence from alcohol, only to reappear when the whiskey was resumed Denman reported a case of pellagra in an alcoholic who drank two quarts of whiskey a day Without change in diet the skin lesions and gastrointestinal symptoms disappeared when the alcohol was discontinued In a few weeks when the patient resumed drinking all the symptoms of pellagra reappeared

The relief of the symptoms when the alcohol was discontinued and the reproduction of the pellagra syndrome after its resumption is positive proof that in these three cases of alcoholic pellagra a known definite toxin, ethyl alcohol, was the primary cause of the disease Whether or not the use of alcohol causes avitaminosis is beside the point, if the patients with alcoholic pellagra had not used ethyl alcohol in beverages, they would not have had the disease, and the symptoms would not have recurred if they had not resumed the use of the toxins In these cases the relief of symptoms did not follow the use of yeast or nicotinic acid, but they subsided when the toxin, ethyl alcohol, was discontinued In passing, it may be added that if one toxin, like ethyl alcohol, the end product of the fermentation of corn and rye, is a known cause of pellagra, why should not other toxins of the phenol group, as those isolated by Lombroso and others resulting from the fermentation of corn, rye, and

other cereals, be one of the predisposing causes of nicotinic acid deficiency, the essential cause of the disease?

The relation of cause and effect between ethyl alcohol and pellagra in alcoholics is clearly established, and alcoholic inebriety produces all the pathologic changes found in pellagra Ethyl alcohol is a known gastrotoxin, in that it will produce acute and chronic gastritis—the latter associated with hypochlorhydria or achlorhydria and enterocolitis is frequent in alcoholics Ethyl alcohol is a known hepatoxin which produces acute and chronic hepatitis—the terminal stages of the latter being called Laennec's cirrhosis Ethyl alcohol is a known neurotoxin, which produces all forms of neuritis from optic neuritis to multiple neuritis It also is an accepted fact that ethyl alcohol is a toxin that causes changes of the cord and brain found in alcoholic insanity of varying degrees from delirium tremens to Korsakoff's syndrome Incidentally ethyl alcohol is a toxin which causes the anxiety neuroses and profound melancholia It is said that 40 per cent of all suicides are due to alcoholism, and the suicidal tendency in pellagrins is well known Ethyl alcohol is a toxin which also affects metabolism It is not unusual to see the obese red faced alcoholic become pale and thin before pneumonia, cirrhosis of the liver, nephritis, pellagra, or other terminal diseases end his miserable life Alcoholics are prone to develop various bilateral skin diseases from simple erythema to generalized eczema, which subside when whiskey and other alcoholic beverages are left off In a recent fatal case of cirrhosis of the liver, before there was ascites, the victim had a red beefy tongue and a severe bilateral erythema of the lower limbs, and to a less extent on the arms, abdomen, and back, which persisted until he was forced to leave off alcohol, when the dermatitis disappeared not to return before his death six months later

Relation of Vitamin Deficiency to Alcoholic Pellagra—It is now the fashion, or the mode, in pellagra investigations to endeavor to make all the phenomena observed in pellagra fit in with vitamin deficiency in food Blankenhorn and Spies surmise that alcohol interferes with the appetite and that the alcoholic pellagrin has starved himself into pellagra, Boggs and Padget suggest "the plausibility of the theory that either

alcohol itself destroys the pellagra-preventing factor in the gastrointestinal tract, or the gastrointestinal tract is altered by the large amount of alcohol that is incapable of assimilating the pellagra-preventing factor."

That there is a deficiency of nicotinic acid, supposed to be the pellagra preventive factor in vitamin B, in alcoholic pellagra there can be little doubt, but Spies and his associates have shown that there is also a deficiency of vitamin B_1 in alcoholic pellagra, and in alcoholism without pellagra, when there is associated polyneuritis. It can be assumed that in alcoholic pellagra, and in the last stages of alcoholism without pellagra, there is a deficiency of all the vitamins, including A and C, as there is in the severe cases of tuberculosis and other wasting diseases. The avitaminosis in alcoholic pellagra is secondary to the abuse of alcohol, and it is secondary to the infection in the severe cases of tuberculosis.

That other forms of alcohol, besides ethyl alcohol, have an affinity for nerve tissue is shown by the outbreak of Jamaica ginger paralysis several years ago. In 1930 a drug firm in Kansas City sent trucks loaded with Jamaica ginger into the rural districts of Kentucky, Tennessee, Alabama, and Mississippi, states in which Jamaica ginger was used as a substitute for whiskey. At least a thousand cases of peripheral polyneuritis, in many of which the victims had bilateral paralysis of the hands and arms, and feet and legs, occurred. Undernutrition, or avitaminosis, was not apparent in any of the patients treated. Seale Harris Jr., investigated an outbreak of "Jake paralysis" that occurred in a town of 100 population in 1930. Of the 8 patients, all gave histories of paralysis that came on in a few days following the ingestion of from one to four ounces of Jamaica ginger. It was supposed that the manufacturer of the alcohol sold to the drug houses had used faulty methods in fermenting sugar or grain and had made isopropyl alcohol, which differs from ethyl alcohol by a few hydroxyl molecules. Certainly it could not be claimed that in these cases the polyneuritis was due to vitamin deficiency, because the paralysis followed in a few hours, or days, after taking the alcohol, and practically all the patients were men in vigorous health when they drank the Jamaica ginger. None of the patients whom we

saw who had polyneuritis following ingestion of "Jamaica ginger" developed pellagra It seems that all of the neuritis following the ingestion of alcoholic beverages, or allied toxins as isopropyl or other forms of alcohol in Jamaica ginger, cannot be due to vitamin B deficiency any more than that the neuritis following encephalitis is due to lack of the antineuritic protective substance

Certainly the victims of alcoholic pellagra would not have developed the disease if they had not become addicts to a habit-forming and toxic narcotic, and no one can deny that ethyl alcohol is not one of the etiologic factors in the production of pellagra

The Genesis of Alcoholic Pellagra—It may be accepted as proved that the two essential factors in the genesis of alcoholic pellagra are (1) the primary cause, ethyl alcohol, and (2) the secondary factor, i e , deficiency of nicotinic acid, the pellagra preventive factor in vitamin B It should be added that nicotinic acid deficiency probably is the one essential factor in both alcoholic and endemic pellagra, but in my opinion there are other factors, both intrinsic and extrinsic, involved in the production of both alcoholic and endemic pellagra

The stomach, intestines, and liver in the order mentioned, are the organs which suffer trauma following the ingestion of alcoholic beverages, particularly whiskey and other concentrated solutions of ethyl alcohol One who has seen alcoholics with cirrhosis of the liver vomiting ropy, glairy mucus knows that chronic gastritis, with achlorhydria, inevitably occurs in chronic alcoholism The morning nausea and vomiting after an alcohol debauch is the beginning of chronic gastritis Undoubtedly secondary infection of the stomach follows, with destruction of the pepsin and hydrochloric acid forming glands Thus Sydenstricker's gastric intrinsic factor which protects from pellagra is lost

The absence of hydrochloric acid in the stomach allows its fermenting contents after a meal to go undigested into the intestines, and chronic enterocolitis is the sequence Since in achlorhydria there is no hydrochloric acid in the duodenum to activate prosecretin, there is a deficiency of the external secretions of the pancreas, and the intestines are filled with a fer

menting mass of undigested chyme Pathogenic bacteria flourish in such intestinal contents, and pathologic changes of the intestines and colon follow

The liver is damaged in chronic alcoholism not only because ethyl alcohol itself is a hepatoxin, but because in the chronic alcoholic it is mixed with toxins formed in the intestines in chronic enterocolitis No doubt secondary infection of the liver occurs in many such cases Mann and Bollman of the Mayo Clinic were unable to produce cirrhosis of the liver in dogs, by ethyl alcohol alone, but they caused hepatitis, the end result of which is Laennec's cirrhosis, by adding other toxins to the ethyl alcohol

I have believed for a number of years that liver pathology is essential in the genesis of pellagra, and also in pernicious anemia This hypothesis was advanced in an article on the etiology of pernicious anemia published in 1926 Recent investigations show that nicotinic acid is present in the liver, according to Sydenstricker as much as 25 mg to 100 Gm of liver, and Sydenstricker suggests that in pellagra the liver cannot store up, or synthesize, this pellagra preventive factor It is known that alcohol is a hepatoxin which in some individuals produces cirrhosis of the liver It also is an accepted fact that a large proportion of autopsies on pellagrins show lesions usually fatty changes, in the liver In other words, in chronic alcoholism there may be the same pathology in the stomach, intestines, and liver as is found in pellagra

Liver Pathology in Alcoholism—I have been impressed with the increase of liver diseases in chronic alcoholics in the last five years, during which time, according to government statistics there has been an unprecedented increase in the consumption of all alcoholic beverages I have had more cases of cirrhosis of the liver in the last five years than I had in twenty previous years I never saw a case of cirrhosis of the liver due to alcohol in a woman until four years ago and since then I have seen five women, all of them of good social standing who have had cirrhosis of the liver In three of the cases there was a marked increase in the size of the liver, also tenderness over the liver and glycosuria Two men and one woman, who had cirrhosis of the liver had what the French

tinic acid, or the nicotinic amides, may be an important factor in the genesis of alcoholic pellagra It is not denied that many alcoholics take little food and no doubt they may suffer also *from nicotinic acid deficiency due to insufficient intake of the* extrinsic pellagra preventive factor

Treatment of Alcoholic Pellagra—"The cardinal principle in the treatment of all diseases is to find the cause and remove it" It, therefore, is evident that in the management of alcoholic pellagra, the use of all alcoholic beverages by the patient must be discontinued If the alcoholic pellagrin is severely ill, it may be best to withdraw the alcohol gradually while treating the pellagra with nicotinic acid and liver extracts parenterally, and orally, if the patient can retain liquids Otherwise the treatment of alcoholic pellagra does not differ from that employed in any form of the disease It should not be forgotten, however, that the alcoholic pellagrin has a permanently damaged stomach and liver, and that the outlook for complete recovery is less hopeful than if there were functional insufficiency of the liver without permanent changes, as seems to be true in many cases of the strictly endemic type of the disease

SECTION II

THE QUEST FOR THE CAUSE OF PELLAGRA
A HISTORICAL REVIEW

CHAPTER IV

EARLY THEORIES ON THE ETIOLOGY OF PELLAGRA

The quest for the cause of pellagra was begun by Don Gaspar Casal, physician to Philip the Fifth King of Spain, when he recognized pellagra as a disease entity in 1735 Casal observed that maize was the chief article of diet of those afflicted with what he called scorbutic leprosy He also noted that the victims "seldom have meat" Casal rejected the idea that pellagra is of atmospheric origin and finally came to the conclusion that the disease develops *sui generis*

Townsend, an English physician, in 1786 and 1787 studied the disease in Spain called scorbutic leprosy by Casal He combated the idea that pellagra is of leprous nature

Solar Theory—Frapolli who in 1771 described the disease in the kingdom of Milan, now a part of Italy, was convinced that what he called '*morbum vulgo pelagra*' was due solely to the effect of the sun's rays

Albera, in 1784, considered exposure to sunlight as the essential factor in the production of pellagra, but suggested that the use of spoiled food may be an underlying factor He also advanced the idea that the use of rancid oils as food may cause pellagra

Inoculation Tests—Gherardini, in 1792 who added an "l" to Frapolli's "pelagra," was the first to make experimental studies in the quest for the cause of pellagra He demonstrated that the skin lesions of pellagra may be brought on by exposure to the sun Gherardini believed at one time that parasites on spoiled food caused the disease though he failed in his efforts to transmit the disease

Buniva (1805 1808) also made the effort to transmit pellagra by inoculation, but failed Two decades later Rolandes confirmed the work of Buniva

Nervous Origin—Videmar, in 1790, first advanced the nervous origin of pellagra He considered it a "variety of hypochrondriasis (*mal del padrone*)" He believed that the skin lesions of pellagra were a variety of impetigo, Videmar also suggested that miasm was a cause

Jansen (1798), an early French investigator, was impressed with, and accepted, Videmar's theory that pellagra is a variety of hypochondriasis

Inanition Theories—Soler, in 1791, was the first to advance the theory of "inanition, the consequence of misery and filth," as the cause of pellagra

Strambio (1794), whom H F Harris regarded as the greatest of all pellagrologists, believed in the *sui generis* theory of pellagra, but he regarded "all depressing influences," including bad food, particularly maize of poor quality, pregnancy, and lactation, as underlying factors

The Maize Theory—Fanzago, in 1807, was the first to make an unreserved claim that pellagra results solely from the use of maize According to H F Harris, Marzari is given the credit for being the first to promulgate the maize origin of pellagra Four years later, in 1814, Guerreschi published his reason for believing that a "fungous growth" on maize is the cause of pellagra

Sette, in 1814, announced his belief in the maize theory of pellagra, and stated that where potatoes were substituted for maize pellagra "ceased its ravages in a short time"

Moldy Maize—Balardini, after many years' study of pellagra from 1845 to 1872, appears to have had much influence in promulgating the moldy maize theory of pellagra Roussel, of France, in his book on pellagra published in 1866, accepted Balardini's spoiled maize theory Roussel is credited by Marie with having eradicated pellagra from France, by being influential enough to persuade French Government officials to issue a decree against raising corn in France When the population of southern France ceased to raise and eat corn and substituted bread made from wheat, barley, and rye, pellagra disappeared

Morelli, in 1855, opposed the view that pellagra is due to corn fungi and advanced the theory that the use of polenta, as almost the sole article of food among the poor in Italy, was the cause of the disease Morelli maintained that maize is not a complete food and that inanition is the underlying cause of pellagra

Insufficient Protein—Lussana and Frua (1857), more than any other Italian pellagiologists, stressed the importance of inadequate food, containing "an insufficient quantity of protein," as the most important factor in the production of pellagra in Italy They also recognized other contributing factors H F Harris reproduced excerpts from Lussana and Frua's monograph on pellagra (pages 122 to 125) which show that those two careful students of pellagra believed that they had attained a comprehensive knowledge of the cause of pellagra Their views dominated the Italian viewpoint of the genesis of pellagra for a generation Lussana and Frua said "We recognize misery and the life of the country as being together the elements which ordinarily cause pellagra Likewise their ordinary food contains an insufficient quantity of protein"

Pellagrazein—Cesare Lombroso, the great Italian criminologist, Professor of Forensic Medicine and Psychiatry in the University of Turin, began his historic studies on pellagra in 1869 He was convinced that corn toxins, "pellagrazein," are the essential etiologic factors Lombroso was the greatest Italian of his time, and he convinced his contreres and his people that he had discovered the true cause of pellagra and that the prevention of the disease consisted of substituting barley and rye bread for polenta (a mush made of corn meal) It is interesting to note that the new Columbia Encyclopedia (1935) credits Lombroso with having "discovered the cause of pellagra"

Theories on the Etiology of Pellagra—So many theories on the causation of pellagra have been advanced that all of them could not be discussed even in a volume devoted solely to the etiology of the disease Therefore, only a relatively few of the most important theories on pellagra can be mentioned and reviewed

Most of the theories on pellagra may be classified into four groups (1) toxins, (2) infections, (3) food deficiencies of quantity and quality and (4) vitamin deficiencies

Toxin Theories

No.	Theory	Authors
1	Toxins in natural corn	Fanzago, 1807 Marzari, 1814
2	Toxins elaborated by corn fungi	Gaeresche, 1814 Balardini, 1845
3	Toxins elaborated from corn smut activated by exposure to sun's rays	Pari, 1870
4	Pellagrazein, a phenol, produced by micro organisms on spoiled corn	Lombroso, 1871 George Searcy, 1906
5	Toxins elaborated by *Aspergilli fumigatus* and *flavus* on corn	Ceni and Besta, 1904 Fossati, 1904
6	Toxic enzymes resulting from fermentation in germinating grain in the spring	Selmi, 1876 Romaro, 1908
7	Toxins elaborated in the alimentary tract from ingested moldy corn	Neusser, 1887
8	Toxins elaborated in alimentary tract from fermenting cane sugar and other carbohydrates	Deeks, 1910
9	Ethyl alcohol in wines, whiskey, and other alcoholic beverages	Calmarza, 1867, Lombroso, 1872, Sarou, 1909
10	Toxins in cheap syrups	Blosser, 1914
11	Chronic intoxication from silicon in colloidal solution in drinking water	Alessandrini and Scala 1913
12	Dioxyphenylalanine ("dopa") a toxin elaborated in fermenting maize and beans	Sabra, 1931
13	Selenium poisoning	Barondes

Infections Theories

No.	Theory	Authors
14	Miasm	Jansen, 1788, Titius, 1791
15	Unknown contagium	Allioni, 1795
16	*Bacterium maydes*	Majocchi, 1881
17	*Penicillium glaucum*	Carraroli, 1902
18	*Streptobacillus pellagrae*	Tizzoni, 1908
19	Mosquito transmission	Thorington, 1908 Roberts, 1913
20	Ameba	Long, 1910, Jelks, 1910

45	Deficiency vitamins A, B, and C	Biggaum, 1937
46	Deficiency vitamin B_2 and intestinal parasites	Ellinger, Hassan and Taha, 1937
47	Nicotinic acid deficiency	Elvehjem, 1937
48	Nicotinic acid deficiency theory applied in the treatment of pellagra contemporaneously in order of first published report of cases	Ruffin and Smith, Spies and associates, Fouts and associates, Sydenstricker, 1937 1938

CHAPTER V

TOXIN THEORIES

George Searcy's Views on the Cause of the First Outbreak of Pellagra in the United States—George Searcy, in his historic report of the first outbreak of pellagra in the United States, in 1907, discussed the corn toxin theory of pellagra. Working on that theory, he stopped the use of corn bread and grits and substituted flour bread and potatoes, making no other changes in the diets of the inmates of the Alabama State Hospital for Insane Negroes, with the result that no other cases developed that year.

No finer example of discriminating investigations on the etiology of pellagra has been made in the United States than were carried on by George Searcy, before he reported his 88 cases. Searcy's classical paper convinced many that corn toxins can cause pellagra, and that the use of corn bread made from musty meal was the cause of the 88 cases at the Mount Vernon Hospital.

The following excerpts from George Searcy's report, published in the *Transactions of the Medical Association of the State of Alabama* (pp. 387-398), 1907, make out a good case for the maize toxin theory. Searcy said:

"A sample of the meal used at the Mount Vernon Hospital, which was supposed to be the best western meal, was sent to the pathologist in charge of the laboratory of plant pathology at Washington and he reported the meal wholly unfit for human use; that it was made of moldy grain and contained quantities of bacteria and fungi of various sorts, some of which were identified.

"*As soon as the nature of the disease was determined and the true cause suspected the patients were taken off corn bread and grits and wheat bread and potatoes substituted. The rest of their diet was continued as before. No new cases except the one in the test case appeared after about ten days. A set of eight patients was kept on the former diet with corn bread and grits as a test. One of these developed the disease, another began to show symptoms, and all became in such poor general health that their diet was changed also.*"

It will be noted that the substitution of wheat bread and potatoes for corn bread and grits prepared from the meal and

grits in which fungi were found, was the only change in diet made by Searcy at Mount Vernon, yet no more cases developed, except the control case in which the musty meal was used This added to the fact that of the 8 who continued the use of the corn meal bread which plant pathologists had pronounced "wholly unfit for human use" 2 developed symptoms of pellagra and the remaining 6 became ill, without definite symptoms of the disease Can evidence be more convincing than that which Searcy produced to prove that corn toxins were factors in producing the 88 cases of pellagra at Mount Vernon in 1906?

It may be mentioned in passing that George Searcy has not been given the credit which he deserved for being the first to produce experimental pellagra in the United States It is reiterated that there is not proof of corn toxins being specific etiologic factors in pellagra, but it seems probable that their role in producing nicotinic acid deficiency lies in their toxic effect on the stomach, intestines, and liver, thus producing gastric and hepatic insufficiency with deficiency of nicotinic acid

Italian Theories—Caesare Lombroso, the great Italian pellagrologist, convinced his European confreres so thoroughly that a toxin found in spoiled maize and other cereal grains was the cause of pellagra that they still adhere to that theory Lombroso's experimental studies in working out the physiologic action of the toxins derived from bad maize, and his production of pellagra like symptoms in animals, by the continued use of those toxins, are fine examples of thorough scientific investigations While Lombroso did not prove his "pellagrazein" theory, his conclusions cannot be disregarded in 1940 in considering corn toxins as one of the many predisposing factors in the etiology of pellagra

In Italy today the opinion prevails that chronic intoxication from toxins produced in moldy corn is the cause of pellagra, and Mussolini's dream of eradicating pellagra in Italy is based largely upon the elimination of corn products from the diet of the Italian peasants He has issued edicts against raising corn in Italy and his government is said to be furnishing the agrarian population of his domain with wheat and barley to substitute for maize as food crops

H F Harris on Corn Toxin Theories—In his monumental monograph, H F Harris collected and commented upon more facts regarding the etiology of pellagra that had been recorded in medical literature for nearly two centuries, than all the other publications that I have been able to find in American and English medical books and journals After such a thorough study of the work that had been done, particularly in Italy, in the quest for the cause of pellagra, the conclusions of H F Harris should be given careful consideration After reviewing the epidemiology of pellagra, showing that it is endemic only in countries in which corn (maize) is the largest component part of the diet of the native population, he summarized the experimental evidence that fermenting or moldy corn produces symptoms and pathologic lesions similar to, if not identical with, those found in pellagra

Lombroso's Experiments—H F Harris' summary of Lombroso's experiments should be read carefully with an open mind, by students of pellagra before discarding the theory that toxins formed in fermenting maize and other cereals are predisposing factors in the production of pellagra He said

'In 1869 the well known pellagrologist Lombroso made a large number of experiments in both men and animals He employed in his investigations fermented maize in the natural condition and also its active principles administered as a tincture and found that 17 out of the 28 individuals upon whom he experimented showed the following extraordinary symptoms belching prostration drowsiness diarrhea pyrosis nausea smarting in the fauces headache hunger insomnia thirst pains in the limbs confusion of ideas sweating dizziness pruritus, and diminution in body weight'

H F Harris, explaining how toxins may cause pellagra in persons who had not eaten corn products, said

Finally we should not forget that the same molds growing on other starches than those of maize produce, beyond question similar poisons which readily offers an explanation of possible cases of genuine sporadic pellagra which might conceivably have their origin in the long continued use for several generations of food products prepared from badly conserved cereals

The discovery of epidemic pellagra in the United States in 1906 followed soon after the studies of Piglini with tinctures made from cultures of *Aspergillus fumigatus*, and after the experiments of Ceni and Besta with toxins from the same

fungus found in spoiled corn had been made Ceni's aspergillus toxin from spoiled corn theory of pellagra was considered the possible cause of pellagra by many American physicians in their early studies of the disease

The National Pellagra Conference in 1912—Babcock and others interested in the study of pellagra raised funds to bring a number of celebrated pellagrologists from the countries of southern Europe to the Conference with the idea that they might give American physicians the benefit of their long experience in dealing with pellagra The opinions of those men on the etiology of pellagra, and the facts which they presented at the conference to show why they believed in the maize toxin theory, should be read carefully by students of pellagra who are seeking the underlying causes of nicotinic acid deficiency

Italian Conception of Corn Toxin Theory—Two of the most distinguished speakers at the National Conference on Pellagra held in Columbia, South Carolina, in 1912, were Drs Gosio and Antonini, of Milan, located in the heart of the Italian pellagra belt Excerpts from their paper present facts which should be known to all who are interested in the etiology of pellagra They gave as their slogan in preventing pellagra in Italy "Combat spoiled corn and all its products" They said

"Of the conception of Lombroso there remains much that is positive in the epidemiological and in the experimental field, in the epidemiological field, because always, even up to the very last days, observers worthy of belief have seen pellagra diminish, even to the point of disappearing altogether, with the single modification of the conditions indicated by spoiled corn, in the experimental field because a great legion of students, still presenting themselves divided in interpretation and in doctrinal formula, always come to find inspiration and support in the same source of facts and proofs which designates the parasites of corn as the recognized cause of the disease, a cause which, up to the present, has enrolled the great majority of forces under a single defensive banner"

Corn Toxin Theory in Rumania—Victor Babes, professor of pathology, Bucharest, Rumania, one of the great European authorities on pellagra, brought a message to the National Malaria Conference in 1912 from the country in Europe which has suffered most from the ravages of pellagra Babes said

"In spite of the rich literature on pellagra, scarcely so important a malady exists about which we are so badly oriented One thing only

seems to be established about its etiology That it belongs to the diseases of poverty, of insufficient alimentation, and notably that it is in intimate relation with nutrition by maize of bad quality To combat the disease successfully therefore, it is necessary to look for other, and more feasible means based upon its etiology With this in view, it is necessary to take account in the first place, of all the serious work which has established the *maidic origin of pellagra* notably, that pellagra as a malady of the people exists only in the countries where the food supply is chiefly corn and especially of the work of those who have proved the disastrous effect of nourishment with spoiled corn Finally, I think I can close this interesting discussion by saying that we are all in accord on the maidic origin of the disease "

Maize Theory in Egypt—Sandwith, who was a speaker at the National Pellagra Conference in Columbia, South Carolina, in 1912, found *that pellagra prevailed among only the maize eaters* in northern Africa He said

'In Egypt and most other pellagrous countries, it is only the poor maize eater who suffers The farm laborer who has to support his family on starvation wages is chiefly attacked a similar laborer earning more regular pay is less victimized while the farmer and the farmer s domestic servants who eat the same varied food as their master, entirely escape "

Corn Toxins and Pellagra in Yucatan—Dr George Gaumer, of Yucatan, Mexico, at the first Conference on Pellagra in 1908, described conditions in Yucatan which he believed were responsible for pellagra in that country His incrimination of American ground corn meal as a cause of pellagra in Yucatan is convincing He said

'Corn being the only cereal used in Yucatan for bread, famine seemed inevitable until the merchants began to import corn from the United States This importation of corn continued until 1891, when the country had recovered from the devastations of the locusts The imported corn was brought from New York in the bottoms of vessels as ballast, and from careless handling and bad storage it was often rendered unfit for food

"From 1891 to 1901 Yucatan produced sufficient corn for home consumption, and new cases of pellagra were no longer to be found, while the old cases ran their course and nearly all of those attacked in the former years died from the effects of the disease From 1901 to 1907 the corn crops were almost total failures and corn was again imported in greater quantities than ever before Most of the corn came from the United States Mobile and New Orleans being the chief sources of supply the remainder coming via Vera Cruz from the interiors of Mexico or nearly the same distance, by water

"Pellagra again became epidemic but was not then confined to the middle and lower classes as in the former invasion The wealthy hemp

owners, on account of the exorbitant prices paid for hemp, found it was more profitable to import than to raise corn for home consumption, thus compelling even well to do people to consume the imported article as the home product was no longer sufficient for the wealthy families. Pellagra spread alike among the rich and the poor, until, by the close of 1907, about 10 per cent of the inhabitants were victims of the disease, and at the present writing not less than 8 per cent of the adult population have pellagra."

Spoiled Corn Theory in Early American Literature on Pellagra.—One finds in the early literature of pellagra in the South that spoiled corn was incriminated often as the etiologic factor, and it seems in some cases that there was evidence to show that musty meal was the cause in the cases reported. First the spoiled meal was found to be the source of the bread used by pellagrins when they developed the disease, and when the bread made from musty meal was eliminated from the diet, immediate improvement in the symptoms followed.

E. J. Watson, Commissioner of Agriculture of South Carolina, in discussing corn meal as a factor in his state at the First National Conference on Pellagra, related the expressed opinions of a number of physicians in his state. He cited one physician as having reported 24 cases. He said they gave a "history of eating store bought or Western meal." A physician in upper Carolina said: "I will state that all cases coming under my observation have been eaters of corn meal and grits."

Watson's investigations showed that some of the Western meal was musty or spoiled. One physician who had treated 10 pellagra patients believed that "eating meal from damaged corn" was the cause. Another physician who had observed 75 cases said that most of them, not all, were traced to impure corn supply. He said: "Those cases under my observation have been consumers of grits and chiefly bread made from corn meal—shipped from the West."

Lavinder and Babcock, two profound students of pellagra, in their book concluded their summary of the various theories of pellagra as follows:

> "It may be said that while the real nature and cause of pellagra still remain in doubt, there is, nevertheless, a firm and almost universal belief that the disease is in some way connected with the use of corn as an article of food—a belief so universal as to render its rejection well nigh impossible except in the face of demonstrative proof to the contrary."

Seasonal Occurrence—The fact that more cases of pellagra occur in the spring months, in March in Florida and in April in Kentucky, has been considered as one of the reasons why it probably is an infectious disease Considering the maize toxin theory as an underlying cause of nicotinic deficiency, may not the fungi which grow in moldy meal become more active as warm weather comes on than in the winter and less active in hot weather? H F Harris cites the observations of Ceni and his associates, and of Gosio and Paladini as indicating that "molds elaborate their toxins only during moderately cool weather, and that in the warmest summer months no poisons are produced at all The facts curiously correspond with the well known tendency of the pellagrous symptoms to appear in the spring and fall, these periods being precisely those during which the mold toxins are the most virulent"

It is probable that mold fungi are always present in the dirty and never washed meal boxes in the homes of the poor whites and blacks who subsist largely on corn bread from year to year When a sack of new meal is brought home it is emptied in the old meal box to become the culture medium for mold fungi that have been in the box for months or years Besides, the meal bought in the country stores in the spring is old meal probably ground the fall before it is shipped into the South, and as the summer and fall come on, the new meal has less of the mold fungi in it

Experimental studies on scrapings from the corners and crevices of meal boxes in pellagrous districts obtained in April or May would seem to be worth while If they contain fungi, extracts from cultures could be made and used to determine whether or not they could cause changes in the stomach, intestines, and liver of undernourished animals sufficient to produce nicotinic acid deficiency Considering all the evidence on the relation of corn toxins to pellagra as recorded in medical literature, it would seem advisable to make experimental investigations on corn toxins as a possible predisposing factor in the production of pellagra

The maize theory as the sole cause of pellagra was abandoned years ago except in Italy and other European countries, but experimental studies are still being carried on which suggest a

possible relationship of toxins in maize and other cereals to pellagra. In a recent article Musser cites the experimental studies on monkeys by Stockman and Johnson. According to Musser these investigators found that "a maize diet caused death in monkeys as a result of central nervous system changes like those of pellagra. An acid was found in maize which, when administered by stomach or hypodermatically, produced the same results." They also found that "other cereals, such as rice, rye, wheat, and oats, produced similar results even when the diet was rich in vitamin containing foods. In rabbits, skin lesions and thinning of bones occurred."

The Relation of Corn Products to Pellagra.—There is ample evidence to prove that corn toxins are not essential etiologic factors in pellagra, but the facts presented in this review of the literature on the maize theories show that pellagra exists almost exclusively in countries in which corn is the principal food crop, and in which the diet of those who have pellagra consists largely of corn products.

In the experimental studies of Lombroso, Ceni, H. F. Harris, George Searcy, and others, the effort was made to show that corn toxins are the sole cause of pellagra. They failed to obtain that objective, but they proved that corn toxins and a diet solely of good corn are deleterious to the health of animals and human beings. Corn toxins, therefore, may be among the many underlying causes, or predisposing factors in the production of nicotinic acid deficiency, the essential cause of pellagra.

There is sufficient evidence to show that a diet consisting solely, or largely, of corn bread made from good meal will produce avitaminosis, particularly nicotinic acid deficiency. I believe that nicotinic acid deficiency to the degree of producing endemic pellagra in the rural districts of the South is due largely to the fact that corn bread is the principal article of diet of those who develop the disease. I also believe that in reducing endemic pellagra to the irreducible minimum in pellagrous areas *the most important problem is to teach the inhabit*ants of the rural districts to grow wheat, barley, and rye, and to abandon the use of corn bread as their principal article of diet. Corn bread in itself is not harmful, unless made from musty meal, but it is deleterious to the health of any one to

use it as the principal article of food, to the exclusion of other foods rich in essential vitamins and minerals

Neusser's Endogenous Toxin Theory—In the late eighties the ravages of pellagra in southern Austria and in Rumania assumed such serious proportions that Neusser, the great Viennese clinician and Professor of Medicine in the University of Vienna, was sent by the Austrian government to investigate the causes of the disease and to recommend measures for its prevention Neusser and his associates made careful studies of the possible etiologic factors He came to the conclusion that the relation of maize to pellagra occurs when the digestion is impaired and fermentation of corn products forms a toxin in the intestines which will produce all the symptoms of the syndrome known as pellagra Neusser's report, 131 pages published in 1887, was an important contribution to the accumulated knowledge of pellagra

Other Toxin Theories—In 1914 Roy Blosser, of Atlanta, advanced the theory that sensitization to cane sugar products, cheap syrups in particular, is one of the factors which may account for the prevalence of pellagra in the South Blosser's experiments on dogs by feeding them on cheap cane syrup mixed with meat and other food were climaxed by the dogs becoming ill and dying He reported remarkable results in human pellagra by eliminating all cane sugar products from the diet of the patients

Alessandrini and Scala, of the Institute of Experimental Hygiene of the University of Rome, advanced the theory that chronic intoxication from silica in colloidal solution in water is the cause of pellagra in Italy McCrary, of Woodbury, Tennessee, very ardently supported the silicon intoxication theory as being the cause of pellagra

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possible relationship of toxins in maize and other cereals to pellagra In a recent article Musser cites the experimental studies on monkeys by Stockman and Johnson According to Musser these investigators found that "a maize diet caused death in monkeys as a result of central nervous system changes like those of pellagra An acid was found in maize which, when administered by stomach or hypodermatically, produced the same results" They also found that "other cereals, such as rice, rye, wheat, and oats, produced similar results even when the diet was rich in vitamin containing foods In rabbits, skin lesions and thinning of bones occurred"

The Relation of Corn Products to Pellagra—There is ample evidence to prove that corn toxins are not essential etiologic factors in pellagra, but the facts presented in this review of the literature on the maize theories show that pellagra exists *almost exclusively in countries in which corn is the principal* food crop, and in which the diet of those who have pellagra consists largely of corn products

In the experimental studies of Lombroso, Ceni, H F Harris, George Searcy, and others, the effort was made to show that corn toxins are the sole cause of pellagra They failed to obtain that objective, but they proved that corn toxins and a diet solely of good corn are deleterious to the health of animals and human beings Corn toxins, therefore, may be among the many underlying causes, or predisposing factors in the production of nicotinic acid deficiency, the essential cause of pellagra

There is sufficient evidence to show that a diet consisting solely, or largely, of corn bread made from good meal will produce avitaminosis, particularly nicotinic acid deficiency I believe that nicotinic acid deficiency to the degree of producing endemic pellagra in the rural districts of the South is due largely to the fact that corn bread is the principal article of diet of those who develop the disease I also believe that in reducing endemic pellagra to the irreducible minimum in pellagrous areas the most important problem is to teach the inhabitants of the rural districts to grow wheat, barley, and rye, and to abandon the use of corn bread as their principal article of diet Corn bread in itself is not harmful, unless made from musty meal, but it is deleterious to the health of any one to

use it as the principal article of food, to the exclusion of other foods rich in essential vitamins and minerals

Neusser's Endogenous Toxin Theory—In the late eighties the ravages of pellagra in southern Austria and in Rumania assumed such serious proportions that Neusser, the great Viennese clinician and Professor of Medicine in the University of Vienna, was sent by the Austrian government to investigate the causes of the disease and to recommend measures for its prevention Neusser and his associates made careful studies of the possible etiologic factors He came to the conclusion that the relation of maize to pellagra occurs when the digestion is impaired and fermentation of corn products forms a toxin in the intestines which will produce all the symptoms of the syndrome known as pellagra Neusser's report, 131 pages published in 1887, was an important contribution to the accumulated knowledge of pellagra

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ditions, the cystine content returned to normal limits A low cystine content was not found in 87 others, normal individuals, cases of syphilis and tuberculosis, and pellagrins, or recent pellagrins, without dermatitis "

Sabra, an Egyptian pellagrologist, announced in 1931 that he had discovered a toxin (dioxyphenylalanine) also called "dopa," of the phenyl group, growing on beans, which he believes to be the cause of pellagra He thinks that the "dopa" toxin also forms in fermenting maize Sabra states that the cheap whiskey consumed by the lower classes of Egyptians contains the pellagra toxin ("dopa") which could account for the high incidence of alcoholic pellagra in Egypt Sabra claims that *sodium thiosulphate will neutralize the pellagra toxin* ("dopa"), and he reports a large series of patients successfully treated with that drug

Barondes suggests that pellagra may be due to selenium poisoning

Other toxins are believed by some to be etiologic factors in the production of pellagra, but proof is lacking that any of them is the one specific cause The opinion seems to be growing, however, that there are a number of toxins which may act as predisposing causes of pellagra

CHAPTER VI

THE RELATION OF INFECTIONS TO PELLAGRA

Findings of the Illinois Pellagra Commission—Pellagra was first recognized in Illinois by L J Pollock in the Cook County Hospital in June, 1909 Dr W A Evans then health officer of Chicago, called in Claude Lavinder of the United States Public Health Service who confirmed the diagnosis During that year (1909), 177 cases were found in the State Insane Hospital at Peoria, Illinois In the years 1909, 1910, and 1911, a total of 408 cases of pellagra of whom 189 patients died, were reported in Illinois Pellagra assumed such serious proportions that the state of Illinois established a commission to study the disease The late Frank Billings was president of the Commission This Commission, consisting of specialists in pathology, bacteriology, entomology, internal medicine, and psychiatry, made a thorough study of pellagra as it existed in Illinois The comprehensive report of the Illinois Pellagra Commission had a profound influence favorable to the infectious theory of pellagra

The study of protozoal infections among the inmates of the Illinois State Insane Hospital at Peoria by Captains Siler and Nichols revealed a surprisingly large percentage of infestations in nonpellagrins (endamebas 52 per cent, flagellates 60 per cent) and in pellagrins 76 per cent, of both endamebas and flagellates Stained specimens were sent to Colonel Charles F Craig, later Professor of Tropical Diseases in Tulane University who confirmed the identity of the endameba and flagellates The pathologic findings of the Illinois Pellagra Commission did not reveal "anything specific, yet there are certain features which seem to be constant and open up certain more or less definite lines for future search "

Pathologic changes in the nervous system were noted in "the Betz and larger pyramidal cells of the precentral convolutions and the cells of the nuclei in the cerebellum, pons, medulla, and cord as well as the posterior root and sympathetic ganglia There was in some cases fatty degeneration in the nervous system similar to that found in senility " They said "the pic

ture is strikingly similar to that of central neuritis" They concluded that "the finding of the nervous system seems to be involved only as a secondary process and at a late stage of the disease"

Constant pathologic changes were found in the liver, which in the light of our present knowledge of the nicotinic acid content of the liver, and the fact that the liver is the storehouse of all the vitamins, suggest that liver insufficiency may be a factor in pellagra in much the same way as pancreatic insufficiency (hypoinsulinism) is the *sine qua non* in diabetes mellitus The liver pathology found by the Illinois Pellagra Commission is discussed in the chapter on the genesis of pellagra It is interesting to note that this Commission of experts regarded the liver pathology as being secondary to intestinal infections They said

> "All these appearances suggest the presence of some toxic substance in the blood One may go even further and from the changes in the intestines and liver, suspect that this toxin originates in the intestines and enters the circulation by way of the portal system"

The conclusions of the Illinois Pellagra Commission were as follows

> "1 Pellagra is a disease due to infection with some living micro organism
>
> "2 A possible habitat for this parasite in man is the intestinal canal
>
> "3 Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease"

I cannot agree with the Illinois Pellagra Commission that pellagra is caused by any one specific micro organism I do believe, however, that many micro organisms causing different and distinctive diseases of the gastrointestinal tract may be factors in the production of pellagra because of secondary damage to the liver

The suggestions of the Illinois Pellagra Commission that further researches should be made in the study of liver pathology in pellagra seem worthy of consideration by investigators on clinical pellagra It would seem desirable to prove that diseases of the gastrointestinal tract may cause liver disease, and secondly to determine whether liver insufficiency is not a factor in nicotinic acid deficiency

The Thompson McFadden Pellagra Commission —The second thorough study of pellagra made in the United States was carried on by the Thompson McFadden Pellagra Commission, from 1912 to 1916, in the cotton mill districts of South Carolina, where pellagra was found to prevail to an alarming extent The investigations were carried out by a number of very competent physicians including Joseph Siler, a surgeon in the United States Army and later a brigadier general in the regular army in charge of medical laboratories of the American Expeditionary Forces in France, W J MacNeal, Director of Laboratories of the New York Post Graduate School, and J F Garrison, a surgeon in the United States Army

The studies of this group included a survey of the food conditions and hygienic environment of pellagrins in the suburbs of, and in the rural districts adjacent to, Spartanburg, South Carolina Their investigations convinced them that food is a factor in the etiology of pellagra only as the vehicle to carry an unknown infection from the excrement of pellagrins into the alimentary tracts of unaffected human beings They suggested that the ordinary stable fly *(Stomoxys calcitrans)*, which is known to carry the *Bacillus typhosus* from the feces of typhoid victims to human food, may transmit the infection of pellagra

The following conclusions summarize the results of the investigations by the Thompson McFadden Pellagra Commission

"1 Pellagra morbidity was higher in congested communities using surface privies than in more sparsely settled districts in which similar methods for the disposal of excreta were employed

"2 In the city of Spartanburg the endemic foci of pellagra were located in the districts in which surface privies were in use

"3 In cotton mill villages equipped with surface privies pellagra was found to be endemic and new cases of the disease arose there year after year

"4 In two cotton mill villages completely equipped with water carriage systems of sewerage disposal it was impossible to find cases of pellagra which had certainly originated there although some cases that had originated elsewhere were present

"5 This study indicates that methods of disposal of human excreta may prove to be a determining factor in the spread of pellagra in certain communities, and it suggests a possible method of prophylaxis which is now being tried in a practical way"

From the standpoint of the spread and location of the disease, the Thompson McFadden Pellagra Commission found that since

1914 practically all the new cases of pellagra in that community developed while the person was residing in the same house with, or next door to, a pellagrin in the active stage of the disease, or within six months after such exposure It was further noted that following the installation of a proper sewage system the spread of the disease was almost wholly arrested, all of which led them to support the infectious theory regarding the spread and outbreak of pellagra

The Thompson McFadden Pellagra Commission, while believing that pellagra is an alimentary tract infection, could find no bacteria or protozoa which may be considered the specific organism that caused the disease They also made repeated unsuccessful attempts to transmit pellagra from one person to another

Jobling's Studies in Nashville —Jobling and Petersen made a study of an epidemic of pellagra that occurred in the suburbs of Nashville Tennessee They traced the origin of a number of cases of pellagra to pellagrins living in the same house, or in houses next door They observed that pellagra was rarely found among the poor in the sewered sections of Nashville, while it was frequent both among the poor and the well to do residents of the suburbs without sewers

Jobling, formerly Professor of Pathology at Vanderbilt University Medical School, and Arnold isolated a fungus from the feces of pellagrins which had distinct photodynamic properties *Cultures of this fungus injected into white mice produced* a pellagra like rash Jobling suggested that toxins produced by intestinal bacteria circulating in the blood may be activated by sunlight, hence, the fact that pellagra is more prevalent in the spring and summer in subtropical countries

Intestinal Protozoan Infestations —John L Jelks, a proctologist of Memphis Tennessee, reported a series of 100 consecutive cases of pellagra in which proctologic examinations revealed lesions resembling those found in amebic dysentery He found flagellates in every case, and he is of the opinion that cercomonads or trichomonads may be specific organisms in pellagra

Dearman, working at Long Beach in the rural districts of Mississippi, found ameba present not only in the stools of pella

grains but reported a number of cases of pellagra with pyuria in which ameba were found in urine specimens

Homer Bruce, of Opelika, Alabama, reported two cases of pellagra which had been previously diagnosed as amebic dysentery and treated as such at a large medical clinic He expressed the opinion that the patients had pellagra first and that the amebiasis was a secondary invasion, though "the two diseases may be closely associated"

Rucker, a neurologist of Memphis, in 1911, advanced a theory, which he also held in 1933 that "pellagra is a gastrointestinal disease infectious in character, and that the skin lesions and nervous symptoms are secondary and due to toxic infection"

Finley's Case of Giardiasis and Pellagra—Theodore Finley, of Washington University, St Louis, reported a case of pellagra in a rural teacher, aged 23 years, who also had a prepyloric ulcer and severe infestation with *Giardia lamblia* He states that this pellagrin's diet which was carefully investigated was "adequate and well balanced" The skin lesions in this case were typical of pellagra the tongue was red and atrophic, and diarrhea was a prominent symptom There was a total absence of free hydrochloric acid in the stomach contents Myriads of *Giardia lamblia* were found on microscopic examination of the duodenal contents obtained through a duodenal drainage Intravenous injections of neoarsphenamine were administered every five days, stovarsol was used orally, and a high caloric diet, with brewers' yeast, was given After six weeks in the Barnes Hospital, after all the symptoms of pellagra had subsided, he had gained 24 pounds, and duodenal drainages revealed no *Giardia lamblia* though a stool specimen showed the presence of a number of encysted parasites Finley cites a number of authors who have reported cases proving that at times the *Giardia lamblia* cases are pathogenic, producing symptoms similar to the intestinal manifestations of pellagra

Soil Pollution—C C Parris, of Fort Worth, Texas, believes that soil pollution is a factor in the production of pellagra In support of that opinion he presents the following facts

"In rural districts where there are no sanitary sewer connections and the open privy is a common source of contaminating the soil with

human excreta, we find the greatest proportion of pellagra In our very large cities where the people are not exposed to the soil, we have little or no pellagra It is one disease that travels from the country towards the cities and stops, so far as origination is concerned, where the cultivation of the soil stops and the sanitary sewer connections begin, or where the soil ceases to be contaminated with human excreta In other words pellagra stops where the cultivation of the soil around the surface privy ends "

The Texas Pellagra Commission—In 1916 a joint Commission, consisting of a number of able clinicians, was appointed by the Texas State Medical Association and the Dallas County Medical Society The report of this committee discussed many phases of the pellagra problem, particularly its etiology and prevention

The following excerpts from the joint report of the Texas State and Dallas County Pellagra Committee deal largely with the infections and soil pollution theories

"There are many reasons to believe that pellagra came to this country direct from Italy and the adjacent countries through immigration

"There is no proof to show that the disease existed here (in Texas) to any extent prior to 1906

"While it is true that in Europe the disease was largely among the poorer classes, this does not hold true in this country and especially is it not true in Texas

"Like many other diseases, a low diet and a run down constitution seem to be predisposing factors That the disease is purely a dietary one is advocated by many, but this theory will not account for all the cases, nor will it explain its sudden incidence and rapid increase in this country

"Many have developed the disease with whose diet no fault could be found

"There is much to support the theory of its being an insect borne disease and the work of the Thompson McFadden Pellagra Commission shows much to indicate that the stable fly *(Stomoxys calcitrans)* may be the carrier

"Some members of this committee believe strongly that an infective agent of the disease may be associated with the soil, especially that polluted by human excreta

"In this connection it is a significant fact that certain investigations have shown the disease to be more prevalent in communities using the unscreened surface privy, and less prevalent in communities having a water carriage sewerage system "

Filtrable Virus Theories—Some very interesting studies in pellagra were made by Dr William H Harris, of New Orleans Tissues from human beings dead from pellagra were

ground with normal saline solution and left on ice over night Then the juice was passed through a Berkefeld filter and the resulting filtrate was injected subcutaneously in large quantities into three monkeys Months elapsed before any symptoms appeared Then in two of the three monkeys typical active pellagra appeared, with the fatal train of symptoms W H Harris concluded from his first studies that the lesson of these researches is, first, that the poison of pellagra can penetrate a Berkefeld filter, second, that it is capable of slow development in an infected system, third, that it can be produced without the intervention of a deficiency diet W H Harris concluded that "these are conclusions too weighty to be accepted from results upon only three animals, yet they are too significant to be dismissed without further investigation "

W H Harris at a later time, applying the same methods he used in his first experiments, injected the spinal fluid of a dead pellagrin into a monkey and failed to produce any symptoms of pellagra His experiments have not been duplicated by others

Dr Beverly Tucker of Richmond concluded from clinical and pathologic studies that pellagra is a virus disease In support of this theory he said

'Let us now consider the possibility of virus infection as the cause of pellagra Among the virus diseases are acute anterior poliomyelitis, smallpox, herpes zoster influenza Pellagra much more resembles these diseases in its acute chronic and recurrent forms than it does scurvy, rickets beriberi, malnutrition and other dietary deficiency diseases Extensive differential diagnoses cannot here be attempted and a brief comparison to acute anterior poliomyelitis shall have to suffice Both pellagra and infantile paralysis have epidemic forms both sweep over large areas of the country but infantile paralysis selects chiefly the colder areas for instance north of the Potomac River, while pellagra occurs south of the Potomac both have seasonal occurrence, both have place (local) incidence infantile paralysis occurs chiefly in childhood while pellagra chiefly in pre mid life adulthood both rarely affect more than one member of a family indicating individual susceptibility both attack the nervous system although in different areas, and both have marked trophic disturbance infantile paralysis mainly in certain muscles pellagra in certain cutaneous and mucous membrane lesions "

Insect Theories—Chilton Thorington, of Montgomery, and Stewart Roberts, of Atlanta, suggested that mosquitoes may

transmit pellagra. Graves, of Waco, Texas, made observations in studying pellagrins and their environment and became convinced that pellagra is a mosquito borne disease. Allan H. Jennings and W. V. King, in 1912, suggested the house or stable fly as possible transmitter of pellagra.

Sambon, of the London School of Tropical Medicine, visited the United States in 1910 and for a time his guess, based purely on surmises without a shred of actual proof, that pellagra is transmitted by an insect, the *Simulium reptans,* the ordinary sand fly, was accepted by many. This phantasy of imagination was soon relegated to the scrap heap of abandoned theories on the etiology of pellagra that has piled higher each decade since Casal first recognized the disease two centuries ago.

Studies on Pellagra as a Spirochete Disease.—The similarity of pellagra to syphilis in many respects, and the fact that it occurs among the negroes and ignorant whites in whom syphilis is a frequent disease, has led to some experimental work to determine whether or not a spirochete is the organism which causes pellagra. The first reported studies on that line were by J. E. Evans, of Fulton, Alabama, who in 1909 made cultures from material taken from the subendothelial capillaries of the dorsal surfaces of the hand of a pellagrin. He found spirochetes in the specimens and came to the "tentative conclusion that pellagra is an 'infectious spirochetosis.'" Evans died soon after the publication of his paper, and no one seems to have *made further studies on that line until in 1928.*

Terrell and Venable, working in the Terrell Laboratories in Fort Worth, Texas, made serologic studies on pellagrins and nonpellagrins. In expressing the hypothesis which led them to undertake their investigations on the etiology of pellagra, Terrell and Venable said: "In support of the theory that pellagra is due to an infectious agent are: First, its peculiar geographic distribution, being confined with rare exceptions to subtropical climates; second, the fact that the numerous instances of epidemics of pellagra can be traced to one or two known pellagrins; third, the history of the spread of the disease is similar to the spread of other chronic infectious diseases; fourth, the remissions and exacerbations characteristic of most cases of pellagra are suggestive of parasitic disease; and fifth, arsenic

has for many years been held to be specific in pellagra as it is in other protozoan diseases such as syphilis and trypanosomiasis. To these we would add a sixth argument in favor of the parasitic theory, and this is that in untreated cases of pellagra, the blood will give a complement fixation reaction."

After repeated blood cultures on pellagrins, Terrell and Venable by aid of the dark field microscope found spirillum like organisms from which they prepared an antigen for making a complement fixation test for pellagra. In preparing the fixation test they followed the Kolmer technique for the Wassermann reaction, using the pellagra antigen.

In studying the sera from 181 patients who had some symptoms suggestive of pellagra, Terrell and Venable made both Wassermann and pellagra fixation tests. "62 were negative to both the Wassermann and pellagra fixation tests, 106 had positive pellagra fixation and Wassermann tests, 13 were positive to both pellagra and syphilis."

The serologic studies on pellagrins made by Terrell and Venable should be followed up by other clinical pathologists who have the opportunity for study of pellagra.

The Transmissibility of Pellagra.—There can be little doubt that pellagra is not communicable directly from person to person, certainly not in the same way that the contagious diseases of known bacterial origin are transmitted. This necessarily does not mean that the essential cause of pellagra is not infectious. Malaria and yellow fever are transmissible only through the intermediate host, a mosquito. Uncinariasis is transmissible but not directly from person to person. Poliomyelitis undoubtedly is transmissible but how or why is not known.

The contagious theory of pellagra was advanced 150 years ago and likewise experiments to prove that the disease is not transmissible from person to person were made by the earliest investigators of the disease. Just who first advanced the contagious theory of pellagra is not revealed from a study of the literature, but Gherardini in 1792, discussed animal parasites as a cause of pellagra, but after an experimental study he became convinced that pellagra is not contagious. Harris cites Buniva (1805-1808) as having made a series of inoculations, presumably of the blood and secretions from pellagrins to non

pellagrins, without having transmitted the disease Some two decades later (1824-1828) DeRolandis, a pupil of Buniva, repeated similar experiments with negative results Medical literature shows that experiments were carried out at various times for a hundred years before pellagra was found in the United States, which proved that pellagra is not communicable directly from one person to another

McCafferty's Experiments—E L McCafferty, who was a student in the Atlanta Medical College, under H F Harris in 1902, was the first physician in the United States to carry out experiments on the transmissibility of pellagra In the first reported epidemic he tried to produce pellagra experimentally in the Alabama Hospital for Insane Negroes He swabbed the mouths of pellagra patients and introduced the secretions and material obtained from the pellagrin into the mouths of healthy inmates without producing the disease He also scraped the skin and "sores" of the hands and feet of pellagrins and rubbed the material into scarified areas of the hands of healthy negroes without any of the subjects acquiring the disease H F Harris himself inoculated nonpellagrins with the blood and secretions of pellagrins without in any case having been able to transmit the disease from one person to another Siler, MacNeal, and Garrison, of the Thompson-McFadden Pellagra Commission, in 1912 to 1916, working on, and believing in, the infectious theory of pellagra, and that soil pollution is a factor in its transmission, were unable after many experiments to transmit the disease directly from a pellagrin to a nonpellagrin

Lavinder, Francis, Goldberger, and Wheeler's Experiments—Lavinder and Francis in 1913 and 1914 failed in many attempts to produce pellagra in monkeys by giving them secretions from the mouth and the feces of pellagrins They also inoculated monkeys with the secretions and excretions and spinal fluid of pellagrins without producing any symptoms of pellagra They likewise failed in their efforts to transmit pellagra directly from pellagrins to nonpellagrins

Joseph Goldberger and Wheeler, in 1915, made efforts to transmit pellagra from one person to another without success In 1916 Goldberger continued the experiments His subjects were 16 normal individuals, including 13 physicians He in

oculated them with the blood of pellagrins and gave them orally the secretions from the mouth, nose and throat, urine and feces of pellagrins He could not produce the symptoms of pellagra in any of the 16 volunteers

The Relation of Infections to Pellagra—It is evident that pellagra is not due to any specific infection, but many observations have shown the co existence of pellagra and many different types of infections, particularly of the intestinal tract It is known that avitaminosis is secondary to many infectious diseases Williams and Spies, in their book on vitamin B_1, have shown that thiamin deficiency occurs in tuberculosis and other diseases Since nicotinic acid is a component factor of vitamin B, it is not unreasonable to believe that during the course of, and following the infectious diseases, nicotinic acid deficiency occurs Reasoning a little further, it may be assumed that among the many underlying and predisposing causes of pellagra are various infectious diseases

It seems probable that infections and infestations of the gastrointestinal tract from the esophagus to the rectum may be predisposing causes of pellagra, because the veins of the lower end of the esophagus, stomach, intestines, colon, and rectum (hemorrhoidal plexus) carry toxins, and in some cases micro organisms, into the liver The liver stores up and utilizes all the vitamins, including nicotinic acid and other components of vitamin B, so that liver damage (insufficiency) from toxins, or infections, may be, probably is, one of the underlying factors in the production of nicotinic acid deficiency, the essential cause of pellagra

CHAPTER VII

FOOD DEFICIENCY THEORIES

H. F. Harris cites Soler as having been the first to advocate food deficiency as the cause of pellagra in 1791. Soler advised the use of protein foods, milk in particular, in the treatment of pellagra. Facheris, in 1804, "first distinctly enunciated the idea that the disease (pellagra) is caused by a lack of animal food." Morelli, in 1855, "subscribed to the theory commonly held by the laity and the great majority of the profession of that period that the affection (pellagra) is due to a lack of good food." Morelli particularly insisted that "the absence of elements of an albuminous character is an etiologic factor of the first importance."

Lussana and Frua, in 1856, said: "Pellagra attacks by preference the peasants, who while subsisting particularly on maize, commonly badly conserved and musty, and on sour milk, are not sufficiently nourished to endure the fatigue of their work and the painful effects of the sun. Likewise their ordinary food contains an insufficiency of protein."

Lussana and Frua claimed to have reduced the mortality from pellagra in northern Italy from 24.5 per cent to 4.5 per cent by improving the diet of 8,000 pellagrins. They also claimed that the increase in food given to their pellagra patients shortened their convalescence by from 20 to 70 per cent.

H. F. Harris found from a study of the literature on pellagra that a liberal diet has been the "sheet anchor" in the treatment from the days of Casal (1762) who advised "good food and milk products." Albera (1779) advised "fresh meat, eggs and milk," Strambio (1824) insisted that animal food was "the *sine qua non*" in the management of the disease. Gherardini (1792) used "meat and abundant food", Fanzago (1809) "animal food", and Lussana and Frua (1856) "nitrogenous food."

H. F. Harris, after citing a number of other authors as having maintained that insufficient food low in proteins is the cause

of pellagra, said "After more than a century of discussion this theory has been rediscovered by Goldberger"

Goldberger's Theory of an Unbalanced Diet Deficient in Proteins as the Sole Cause of Pellagra—To Joseph Goldberger, of the United States Public Health Service, should be given the credit for promulgating the theory of "an unbalanced diet, low in proteins," as the cause of pellagra in the South Goldberger was a dreamer and a man of action who tried to make his dreams of a pellagra free United States come true

Soon after Joseph Goldberger was placed in charge of pellagra prevention in the United States Public Health Service in 1914 he became impressed with the idea that it is a dietary deficiency disease It was on this hypothesis that he suggested to Lorenz and Willetts that they treat a number of cases of pellagra in the Georgia State Sanitarium (for the insane) exclusively by improvement in diet, without the use of medicine The results were so successful that Goldberger decided to make further studies in curing and preventing pellagra by diet alone

During the spring and summer of 1914, assisted by Waring and Willetts of the United States Public Health Service Goldberger observed 205 cases of pellagra in two orphanages in Jackson, Mississippi No change was made in hygienic or sanitary conditions They added 2 cups of milk, eggs, beans, and peas to the daily diet, and the carbohydrate content was reduced Of the 205 patients, 172 had no recurrence of symptoms for a year and in only one who continued the diet did symptoms recur

Of the 72 patients in the Georgia State Insane Hospital who were cured by improvement in diet, not one had a recurrence of symptoms after one year

Goldberger and Wheeler's Pellagra Squad—In February, 1915, Goldberger and Wheeler organized a "pellagra squad" consisting of 11 convicts in the Mississippi penitentiary at Jackson, Mississippi All were white and none had histories of previous attacks of pellagra It should be added that no cases of pellagra had been found among the other convicts

Goldberger and Wheeler said that "of the eleven volunteers not less than six developed symptoms, including a typical dermatitis, justifying a diagnosis of pellagra Loss of weight and

mild nervous symptoms appeared early The gastrointestinal symptoms were slight Definite cutaneous lesions did not develop until September 12, or about five months after the beginning of the restricted diet In all six cases the skin lesions were first noted on the scrotum Later the eruption also appeared on the hands in two cases, and on the back of the neck in one The scrotal lesions conformed to the type described and figured by Merck and also by Stannus"

It will be noted that no mention was made of mouth symptoms nor of the presence of the characteristic pellagra tongue

Goldberger and Wheeler did not assert at that time that pellagra was due to "an unbalanced diet deficient in proteins" but considered the diets "faulty"

When physicians who had large experience in treating pellagra read Goldberger and Wheeler's description of their experiments *in the United States Public Health Reports* late in 1915, and in the *Journal of the American Medical Association* on February 12, 1916, many were not convinced that the 6 convicts had pellagra, and they so expressed themselves

Among those who questioned the diagnosis of pellagra in the Mississippi convicts may be mentioned a number of clinicians who were prominent in 1916, and later, because of their studies on pellagra, including W L MacNeal, director of the Department of Laboratories, New York Post Graduate Medical School and a member of the *Illinois Pellagra Commission (1909 1911)* and the Thompson McFadden Pellagra Commission (1912 1914) (J A M A 66 975 977 March 25, 1916), H F Harris, Professor of Pathology, Atlanta Medical College and State Health Officer of Georgia (*Pellagra,* Macmillan, 1919), Isadore Dyer, Professor of Dermatology and Dean of the Tulane Medical School, C C Bass, Dean of Tulane Medical School (Southern Med J 1916), Deaderick and Thompson, Hot Springs, Ark (*Endemic Diseases in the South,* W B Saunders Co 1918), the late H S Thatcher, Professor of *Pathology,* University of Arkansas, Little Rock (Southern Med J, 1932), J S McLester, Professor of Medicine, University of Alabama, Birmingham, Alabama (Ann Int Med 8 459, 1934), John L Jelks, Memphis, Tenn, author of many articles on pellagra, the late

W A Dearman, Gulfport, Miss, well known because of his researches on pellagra, Percy Wall, President of the Mississippi State Medical Association, J W Eckford, Starkville, Miss, and W J Aycock, Calhoun City, Mississippi (personal communications)

Goldberger and Tanner Asserted in 1922 That Vitamins Are Not Factors in the Production of Pellagra—Goldberger held on to the amino acid deficiency theory until after 1922 He and Tanner in an article entitled 'An Amino Acid Deficiency as the Primary Factor in Pellagra'' (J A M A, 1922), reported 5 patients with pellagra in whom there were recurrences of the symptoms in all 5 patients in spite of the fact that for two and one half months they had been given adequate quantities of all the known vitamins They concluded that vitamin deficiency could not have been a factor in producing the pellagra syndrome They reiterated at that time, in 1922, their opinion that amino acid deficiency is the essential factor in the production of pellagra

It will be noted that in 1922 Goldberger and Tanner used yeast, tomato juice, and cod liver oil in their experimental studies to prove that pellagra is not due to vitamin deficiency In spite of the use of what they regarded as sufficient quantities of the "known vitamins," there was a recurrence of pellagra in 5 patients on diets low in proteins (amino acids)

Goldberger's Contributions in Preventing Pellagra—While Goldberger's amino acid deficiency theory as the sole cause of pellagra has been replaced by his pellagra preventive factor in vitamin B deficiency hypothesis, he was right in predicating that insufficient food is the most important etiologic factor in pellagra There cannot be any doubt but that the practical application of the food deficiency theory cured and prevented many cases of pellagra in the United States It also is certain that Goldberger did a great deal of good in promulgating his theory and in his personal efforts in many outbreaks of pellagra in the states in which it is endemic

Goldberger's educational work, in teaching the necessity for adequate diets, improved the health conditions, and prevented many cases of pellagra, in the eleemosynary institutions all over the United States To a great extent he was responsible for

larger appropriations for the maintenance of many state institutions for the care of the insane, blind, and deaf Orphanages, almshouses, and other institutions for the care of dependents and indigents made provisions for better food and more varied diets as a result of Goldberger's efforts

Goldberger and Grote in Alabama.—One instance will be mentioned showing the results of the practical application of Goldberger's food deficiency theory and of how he aided public health officials in controlling outbreaks of pellagra Among the first full-time county health officers in Alabama was Carl Grote, now an internist in Huntsville As health officer of Walker County, Grote was called upon by W H Cunningham, then of Corona, a mining town near Jasper, to aid in controlling an epidemic of pellagra that had developed among miners State Health Officer Welch invited Joseph Goldberger, then pellagrologist for the United States Public Health Service, to go to Walker County to aid County Health Officer Grote in controlling the epidemic The patients under treatment were cured by the Goldberger diet, and other cases were prevented by providing better food and better living conditions Grote and Cunningham, the latter was recently president of the Alabama State Medical Association, were convinced by their experience that Goldberger's theory of an unbalanced diet deficient in proteins was the cause of pellagra Grote's article describing this outbreak of pellagra, published in the *Southern Medical Journal*, was a forceful plea for the adoption of Goldberger's methods in the treatment and prevention of pellagra

Grote's conclusions summarize the practical application of Goldberger's deficient diet theory in curing and preventing pellagra They are as follows

"From all of the evidence that we have been able to gather in Walker County we believe that the following conclusions are justified

1 Well nourished people do not have pellagra

2 The diet of our backward farmers, and farmers who have moved to the mining camps, has undergone a serious deterioration in nutritive value during the past few decades

3 In our cases of pellagra there is the sameness of diet, excessive in carbohydrates and deficient in nitrogenous elements

4 Pellagrins as a class do not own cows, consequently are deprived of milk

5 A well balanced nutritious diet in addition to almost any medical treatment with its psychic effect will cure most cases of uncomplicated pellagra

6 It is the duty of our boards of health to teach and demonstrate to the masses that pellagra can be cured and prevented "

The medical literature on pellagra in the United States from 1915 to 1925 consists largely of reports of outbreaks controlled by adopting Goldberger's methods, and of papers reciting the reduction of the incidence of pellagra in insane hospitals in many states Whether or not one believes that Goldberger and Wheeler produced pellagra experimentally in the Mississippi convicts is not of material importance, and the fact that Goldberger did not prove that pellagra is due solely to diets deficient in proteins is only of historic interest, there can be no doubt, however, but that the practical application of the methods of preventing and curing pellagra as promulgated by Goldberger has had more to do with reducing endemic pellagra in the South than any other single factor This contribution to the welfare of the Nation and Goldberger's investigations proving the existence of a pellagra preventive factor in vitamin B fix his place in history as the foremost American pellagrologist

Deeks' High Carbohydrate Diet Theory—Deeks' theory of the genesis of pellagra deserves more than passing consideration Deeks, a Canadian was a very able clinician with a flair for nutrition He was associated with General Gorgas in the sanitation of the Canal Zone, and was Physician in Chief of the Ancon Hospital Later Deeks served for many years as Medical Director for the United Fruit Company This company has more than 100,000 employees in tropical America and the West Indies, and maintains modern well equipped hospitals for its employees in Cuba, Jamaica, Guatemala, Honduras, Costa Rica, Panama and Columbia Deeks' first thought was the prevention of disease in the tropics, and with the hearty cooperation of carefully selected, well trained physicians, he cared for the health of at least half a million people, consisting largely of native American Indians and the descendents of Indians who married Spaniards and a comparatively few white Americans This native population, largely without education, was living in tropical countries under the worst possible hygienic conditions when the United Fruit Company went into the Amer

ican tropics to develop the banana industry, now one of the largest and one of the most important industries in the world

As a guest of the United Fruit Company, I was a delegate to the International Conference on Health Problems in Tropical America held at Kingston in 1925, and spent two months in visiting the United Fruit Company's hospitals and in investigating food conditions in Cuba, Jamaica, Guatemala, Honduras, Costa Rica, and Panama "*The conquest of the American tropics*" by the United Fruit Company has transformed many tropical jungles, formerly reeking with malaria, amebic dysentery, filariasis, hookworm, and other tropical diseases into well ordered communities, with morbidity and mortality rates comparable to those of the cities of the United States I therefore am in position to know of Deeks' work on pellagra and other food deficiency diseases in the American tropics

Deeks on High Carbohydrate, Vitamin Deficient Diets—Deeks in studying diseases in the tropics investigated the food habits of the native population, as well as those of the Fruit Company's employees from the United States, and he came to the conclusion that the most important underlying cause of disease *in the tropics is an inordinately high carbohydrate, insufficient vitamin,* diet, not only of the natives but also of the foreign population of the West Indies and Central America

Deeks, when chief of the medical service of Ancon Hospital, had the opportunity of studying a number of cases of pellagra, from 1907 to 1912, and at the National Conference on Pellagra at Columbia, in 1912, he read the first of a number of papers on his theory that a high carbohydrate diet, of cane sugar products in particular, was the underlying cause of pellagra, and that a low carbohydrate diet, eliminating cane sugar products altogether, is the best method of treating the disease

Deeks believed with Neusser, though his conclusions were arrived at independently, that toxins formed in, and absorbed from, the intestinal tract affect nutrition, resulting in pellagra and many other diseases Deeks postulated, though he admitted that it has not been proved, that in the process of evolution man has become *biologically unable to digest* and metabolize an excess of purified and devitaminized cane sugar products, and other devitaminized carbohydrates as white flour,

white meal, and white rice He believed that when an excess of carbohydrates was ingested daily over a period of years the first effect is gastric and intestinal digestion, and that as a result fermentation of food begins in the stomach and increases in the intestines As a result of the bacterial activity in the intestines, toxins, such as the aldehydes and the kindred groups of alcohols, are formed, and as a sequence, there is infection of the gastrointestinal tract, i e, gastroenterocolitis

Deeks also believed that hepatitis followed the gastroenteritis and that the resulting damage to the liver affected general nutrition He also believed, what was later proved by McCarrison, that ulcers of the stomach, gall bladder infection and colitis and other abdominal infections may be caused by high carbohydrate, vitamin deficient diets

Recent Investigations on the Relation of High Carbohydrate Diet to Vitamin Deficiency—It is interesting to note that recent investigations seem to show that vitamin B deficiency, in probably all of its eight or more component parts, is related to carbohydrate metabolism, *and that a deficiency of vitamin B_1* in particular prevents proper metabolism of carbohydrates There also is evidence to show that vitamin B_1 deficiency affects the normal balance between glycogenesis and glycogenolysis, probably by its effect on the endocrine system, particularly the islet cells of the pancreas and the suprarenal glands Williams and Spies state that "there is convincing evidence of frequent disturbance of glycogen storage and blood sugar in avitaminosis", and they cite the studies of Levinson and others to show that "vitamin B_1 deficiency leads to a disturbance of carbohydrate metabolism quite apart from that caused by inanition, and that this carbohydrate disturbance precedes the nervous symptoms in vitamin B_1 deficiency"

This recent work, showing that vitamin deficiency results in disturbed carbohydrate metabolism, fits in with the ideas of Deeks, who tried for years to impress upon the medical profession of America the health hazards of diets consisting largely of white flour, white meal, white rice and white sugar products and other devitaminized foods Deeks believed, however, and he probably was right in his conclusions, that toxins formed in the intestinal tract are the primary and the most important

cause of the avitaminosis resulting from high carbohydrate diets, of cane sugar products in particular

Goldberger and Wheeler in the publication of their "unbalanced diet, low in proteins" theory of the cause of pellagra in 1916 failed to mention the similar theory advanced by Deeks in 1912

Deeks' "high carbohydrate diet" theory was essentially an unbalanced diet low in proteins, which Goldberger later called his "pellagra productive diet", and Deeks' treatment of pellagra with diets low in carbohydrates and high in proteins was essentially the same diet advised by Goldberger in his "cure" for pellagra It also is interesting in the recent ideas on low carbohydrate diets in pellagra to observe that no credit has been given to Deeks and the Italian investigators of the last two centuries, who have at various times advanced deficient and improperly balanced diets as the cause of pellagra All of which goes to show that in making investigations of the various phases of pellagra a knowledge of the literature in two centuries of experience with the disease may be helpful to those now studying pellagra It may be added that one of the motives for preparing this book is to make available to students of pellagra a résumé of what has been accomplished by many investigators of the disease in Europe and America

If Deeks is right in his postulate of intestinal toxins resulting from a high carbohydrate diet as the primary cause of pellagra, its genesis should be about the same as that of the exogenous toxin, ethyl alcohol, the underlying factor in the production of alcoholic pellagra

CHAPTER VIII

EXPERIMENTS ON ANIMALS IN THE QUEST FOR THE CAUSE OF PELLAGRA

Lombroso, Gosio, Antonini, De Pietro, Ceni, Costa, and many other Italian pellagrologists used dogs in efforts to produce experimental pellagra. A study of the reported results of Lombroso and his associates with the use of a toxin, called "pellagrazein" in dogs is not convincing that the animals had pellagra, though they became ill and died during the experiments. The autopsy findings in the dead animals showed changes in the gastrointestinal tract and nervous system, particularly of the spinal cord, analogous to those found in fatal cases of pellagra in human beings. Lombroso was convinced himself, and he convinced his confreres and the Italian people, that he had produced experimental pellagra in dogs, and that he had proved his theory of toxins formed in moldy maize as the cause of pellagra.

When pellagra was found to be endemic in the United States in 1907, the historic experiments of Gosio, Antonini, De Pietro, Ceni, and Costa, begun in 1899, were being concluded. These groups of investigators made many experiments on dogs to prove that toxins derived from corn mold, particularly that formed by the aspergilli and penicilli, were the cause of pellagra. A number of American students of pellagra, including Babcock and Watson of Columbia, South Carolina, Stewart Roberts and H. F. Harris of Atlanta, and Herbert Cole of Mobile, visited Italy from 1908 to 1912, and they, particularly Babcock, H. F. Harris and Cole, were impressed by the experimental investigations of Lombroso, Ceni, and Costa. Thus it was during the first decade, from 1906 to 1915, of endemic pellagra in the United States, that the corn toxin theories of pellagra of Lombroso and Ceni were generally accepted.

Bass, in 1910, was much impressed with the experimental studies on mice by Raubitschek, who fed white mice on polenta made from good and spoiled maize. The mice which were exposed to sunlight became ill, and died, having symptoms and skin lesions which he thought were analogous to pellagra in human beings, while the mice fed on the same diet but not

and Mendel and Goldberger and Wheeler This Committee which consisted of Henry C Sherman, Professor of Food Chemistry, Columbia University Chairman, D F Jones, T P B Jones, E L Fisk, and C E A Winslow, was much impressed by the Yale experiments

Experimental Studies on Dogs by Goldberger and His Associates—The first published report of studies on blacktongue by Goldberger and his associates was in 1922, seven years after Chittenden and Underhill's report of their experimental production of "blacktongue" in animals on a deficiency diet Wheeler, Goldberger, and Blackstock then called attention to the striking similarity and probable identity of Chittenden and Underhill's pellagra-like syndrome in dogs and the condition known to American veterinarians as "blacktongue" There is, they (Wheeler, Goldberger, and Blackstock) declared "the possibility, if not the probability, that blacktongue in dogs may prove analogous to pellagra in man" They said "Blacktongue seems to have a geographic distribution in the United States singularly like that of pellagra Seasonally it is reported to occur more frequently in summer and autumn and to affect cur dogs less than those of higher grade There is some evidence that it may occur more than once in the same animal"

Goldberger and his associates produced "blacktongue" in dogs, a disease which they believe to be analogous to or identical with, pellagra in man, by feeding them on balanced diets, so far as carbohydrates, fats, and proteins were concerned, but deficient in the pellagra preventive (P P) factor Having produced "blacktongue" in dogs they then cured the animals which remained on the same diet, by giving them yeast, which is known to be rich in vitamin B

Further studies by Goldberger and his associates convinced them that vitamin B contained two factors one the known antineuritic (anti beriberi) factor and another the pellagra (P P) factor also called vitamin G

The nomenclature of the pellagra preventive factor, a term coined by Goldberger, has been confusing When it was found that Funk's vitamin B may be divided into several fractions, each having a distinctive function, the nomenclature for the pellagra-preventive factor adopted by British biochemists was

vitamin B_2, while vitamin G was adopted by a Committee on Nomenclature appointed by the American Society of Biological Chemists for the same factor in vitamin B, the terms vitamin B_2 and vitamin G have become obsolete as the pellagra preventive factor

Sebrell's Summary of Investigations by Goldberger and Associates—While Goldberger has been given the credit largely for the work done on pellagra by the United States Public Health Service, he was fortunate in having associated with him a group of able and loyal confreres who deserve distinction for their earnest and meritorious studies, proving the importance of the food factor in the etiology, prevention, and cure of pellagra Wheeler was associated with him from the time of his early experiments Voegtlin also worked with him for many years Later Sebrell, Lillie, Rogers, Tanner, and Onstatt were associated with him in his nutritional studies with blacktongue in dogs and pellagra in human beings W H Sebrell, a worthy successor to his former Chief, Joseph Goldberger, is now in charge of the pellagra activities of the United States Public Health Service Sebrell in a "special article" published in the *Journal of the American Medical Association* summarized the recent work on the pellagra preventive factor in vitamin B The following excerpt from Sebrell's article summarizes the conclusions deduced from the investigations by Goldberger Sebrell, Wheeler, and their associates

"The term pellagra preventive or blacktongue preventive factor is applied to the substance originally postulated by Goldberger and Tanner as necessary for the prevention of human pellagra There is no confusion with regard to the substance referred to when its definition is restricted to this meaning Whether or not any of the other later identified fractions of the vitamin B complex are identical with this one is problematic as indicated in the preceding discussion Whether a deficiency in this factor will produce a symptom complex in rats or in any other experimental animals other than dogs remains to be demonstrated, and tests with pellagra or blacktongue are the only sound experimental methods for work on the pellagra preventive vitamin at the present time Human experiments served a very useful purpose before a suitable experimental animal was available and yielded information of immense value which could have been obtained in no other way Goldberger and Wheeler and their associates conducted a long series of preventive tests on man These experiments were conducted by adding the foodstuff to be tested to a known pellagra producing diet and feeding this supplemented diet to a group of subjects If pellagra

hours the dogs were unable to stand on their feet Bradycardia and cardiac arrhythmia of the sinus type were noted Coma developed rapidly and death occurred from respiratory failure within twelve hours The animals could be revived dramatically by the intravenous use of adequate doses of riboflavin if given before the lethal symptoms appeared

The pathologic changes in the liver of dogs dying of ariboflavinosis, as described by Sebrell and Onstott, are constant and characteristic The liver was not enlarged but of a yellow color with red lobular markings The liver cells contained yellow fat globules The changes in the other organs were not constant and mainly those found in animals dying of black tongue, which Sebrell considered as a complicating factor in the ariboflavinosis in dogs

Sebrell also recognized ariboflavinosis as a disease of human beings, *occurring at times independent of*, but frequently associated with, pellagra as a complicating factor Sydenstricker, Spies and others, including myself, have recognized ariboflavinosis in human beings associated with and without, pellagra

Sebrell in an address on "Nutritional Diseases in the United States" at the meeting of the American Medical Association, June 12, 1940, expressed the opinion that many cases diagnosed as mild pellagra, or pellagra sine pellagra, are due to riboflavin deficiency He mentioned, as characteristic lesions of ariboflavinosis, fissures in the angles of the mouth, scaly red lips, magenta colored tongue, and a seborrheic dermatitis in the nasolabial folds and around the inner and outer canthi

Sebrell also called attention to the eye manifestation of riboflavin deficiency, particularly keratitis and corneal ulcers, which disappear after the oral administration of from 5 to 15 mg of riboflavin daily for a few days Sebrell cited Spies as having *observed conjunctivitis in riboflavin* deficiency and quoted Sydenstricker as having reported 47 cases in which eye manifestations were present

Investigations on Canine Pellagra at Duke University—The experimental work on pellagra at Duke University has been outstanding in thoroughness and scientific accuracy The studies of David T Smith, Elbert L Persons, and Harold I

Harvey of Durham North Carolina on the identity of the Chittenden Underhill Mendel "blacktongue" in dogs and the Goldberger Wheeler canine "blacktongue" seem to show "that the clinical picture of blacktongue appears in both types of the experimental disease", but that "the Underhill Mendel type is probably due to a vitamin A deficiency, while the Goldberger type is the analogue of true pellagra in man"

It is interesting to note that Smith, Persons, and Harvey found a "secondary fusospirochetal infection" both in the Yale and Washington types of blacktongue It appears more than a coincidence that Spies and others have found the presence of Vincent's spirillum in the stomatitis of both alcoholic and endemic pellagra

The author, however, does not believe that there is any one specific organism which causes pellagra in animals or in human beings, but he does believe, with McCollum, that avitaminosis lowers resistance to the invasion of all pathogenic organisms, and it seems possible that the pellagra producing diets may cause the disease in both animals and human beings, first by the gastroenteritis following avitaminosis As a result, toxins formed in the intestinal tract are carried from the intestines into the portal circulation and produce liver damage to the extent that certain, as yet unknown hepatic cells lose their power to store, or utilize, nicotinic acid In gastroenteritis following avitaminosis, the pathogenic organisms themselves may be carried to the liver, and as a result of a subacute or chronic hepatitis changes in the liver occur which prevent or inhibit, the cells from storing or utilizing nicotinic acid

Mellanby's Double Vitamin Deficiency Theory—E Mellanby in an article entitled "The Experimental Production and Prevention of Degeneration in the Spinal Cord" (Brain 54 1 247, 1931) described experiments by which he produced spinal cord changes in rabbits, analogous to those found in human pellagra, by feeding them diets deficient in vitamin A He also prevented the cord changes in animals fed on diets deficient in the pellagra preventive factor by giving them sufficient quantities of vitamin A

Mellanby concluded that "vitamin A, or carotene, may play a part in the prevention of pellagra, or at least its nervous mani

esting Whether these compounds are equally effective in human pellagra can only be answered by clinical trials "

Within a few weeks after the publication of Elvehjem's paper announcing that nicotinic acid had cured blacktongue in dogs, and suggesting its use in human pellagra a number of investigators working independently, but contemporaneously, proved that the drug will cure and prevent human pellagra It, therefore, seems evident that nicotinic acid is the pellagra preventive factor in vitamin B, and that the essential cause of pellagra is a deficiency of nicotinic acid Thus it was that animal experimentation by Elvehjem and his associates in the University of Wisconsin marked the beginning of the end in the quest for the essential cause and the cure of pellagra Elvehjem and his dogs will go down in medical history with von Mehring and Minkowski and Banting and the dogs used by them in proving the pancreatic origin of diabetes mellitus

I would not leave the impression that there is no need for further animal experimentation on pellagra On the contrary I feel that the discovery of nicotinic acid as the pellagra preventive factor in vitamin B is but the beginning of experimental studies to prove the underlying pathologic causes of nicotinic acid deficiency Many such studies suggest themselves to me, the most important, and perhaps the most difficult of which are experiments to prove, or disprove that liver insufficiency with, and without, hepatic pathology is an intrinsic factor in the etiology of pellagra

CHAPTER IX

VITAMIN DEFICIENCY THEORIES

Funk's Hypothesis of Vitamin Deficiency as the Cause of Pellagra.—Following his epoch making nutritional studies in 1910 and 1911 by which he proved that beriberi is a food deficiency disease, due to the lack of a protective substance which he called "vitamine," Casimir Funk expressed the opinion that vitamin deficiency may be the cause of pellagra. It also is interesting to note that more than a quarter of a century ago in an attempt to isolate the anti beriberi vitamin from yeast, later designated B_1, Funk isolated nicotinic acid which he used and found ineffective in treating polyneuritis in pigeons.

Funk found that whole yeast was effective in treating polyneuritis in pigeons, but that nicotinic acid, which he isolated from yeast, did not contain the anti neuritic factor. Funk isolated three fractions from yeast, one of which was nicotinic acid, and he found that the combined fractions gave better results in treating polyneuritis in pigeons, than when his crude crystalline product "1" was used alone. Thus it will be seen that for more than twenty five years it was known that vitamin B contained several factors. Casimir Funk not only predicated the vitamin deficiency theory of pellagra, but he laid the foundation for its treatment with yeast and nicotinic acid.

Funk also proved that what he called the antineuritic vitamin might be divided into three fractions. The fact that recently vitamin B has been found to be made up of many nutritional factors extends the studies made by Casimir Funk in 1911 and 1912. It therefore appears that Casimir Funk left little to discover, either as to the cause and cure of pellagra, by the later proponents of the pellagra preventive factor theory, or to the use of yeast and nicotinic acid in its treatment.

For further illuminating information on Funk's vitamin B studies the student of pellagra is referred to Funk's article on "The Etiology of the Deficiency Diseases" (J. State Med. 20

341, 1912, the J Physiol 46 173, the Brit M J 1 814, 1913), and to Funk's statement on "Nicotinic Acid and Vitamin B" (J A M A 109 2085, 1937)

Rupert Blue on Vitamin Deficiency on Corn Bread Diet—Surgeon General Rupert Blue of the United States Public Health Service in an address opening the second meeting of the National Association for the Study of Pellagra in Columbia, South Carolina, in 1912 called attention to Funk's hypothesis that pellagra is due to vitamin deficiency Blue suggested that a diet consisting largely of corn products is deficient in vitamins In my opinion Surgeon Blue's suggestion that vitamin deficiency is due to the use of corn meal products went further towards accounting for pellagra in the South than the theory of unbalanced diet low in proteins General Blue said

"A second promising line of investigation as regards the causation of the disease is to be found in the deficient theory as advanced by Casimir Funk He states that 'it is beyond any doubt that pellagra has some close connection with maize diet' Pellagra is thus placed in the same category with scurvy and beriberi It is only in the case of an exclusive or one sided diet of corn, and, if the corn is spoiled, it is all the more deficient in nutritive values

It will be seen that the corn doctrine of the 'Zeist' school is not entirely rejected nor is it confirmed by the researches of Dr Funk It means that if corn either spoiled or sound, is used as an exclusive diet, certain symptoms will appear Similarly, if a rice diet is persisted in, the syndrome known as beriberi will follow"

Sandwith on Pellagra as a Vitamin Deficiency Disease—F M Sandwith, the English pellagrologist, who made noteworthy studies on pellagra in Egypt, at the meeting of the National Pellagra Conference in 1912, predicated both the vitamin deficiency and the amino acid deficiency theories of pellagra He also suggested that a specific hormone may be a factor in pellagra He said

'Scurvy, epidemic dropsy and rickets are all diseases due to some deficiency of nutrition, but capable of cure if that deficiency be banished from the diet

"Is pellagra, too, a deficiency disease, waiting for a 'Vitamine' to be discovered?

"A few years ago Dr F G Hopkins wrote a paper to teach us that a dietary containing zein as its only nitrogenous constituent, is unable to maintain growth in young mice, but the addition of tryptophane (an amino acid absent from the decomposition products of zein) to such a dietary greatly prolongs the survival period of animals fed on

zein, and materially adds to the well being of such animals It is suggested in the joint paper from which I quote, that the tryptophane is directly utilized as the normal precursor of some specific 'hormone' or other substance essential to the processes of the body "

Funk's vitamin deficiency theory of pellagra seems to have been discussed in pellagra circles for a time and then forgotten I can find in the literature nothing more than casual references to the possibility of pellagra being a vitamin deficiency disease until in 1917, when Chittenden and Underhill produced black tongue in dogs by feeding them on diets deficient in vitamin A They suggested that blacktongue in dogs is analogous to pellagra in human beings

Goldberger's Pellagra Preventive Factor —After abandoning the "unbalanced diet, deficient in certain amino acids" theory as the cause of pellagra, Goldberger, working on the hypothesis of vitamin B deficiency in pellagra, advanced by Funk in 1912, came to the conclusion about 1923 that a specific deficiency, what he called "the pellagra preventive factor" in vitamin B, is the cause of pellagra Later Goldberger and his associates succeeded in producing blacktongue in dogs on diets with adequate quantities of the anti beri vitamin, now called B_1, but deficient in another fraction, the pellagra preventive factor, of vitamin B

The epoch making experiments by Goldberger, Wheeler, Sebrell, and others in proving that a deficiency of the pellagra-preventive factor in vitamin B is essential for the production of blacktongue in dogs are described in the chapter on "Experiments on Animals " Following the really fine researches of Goldberger and his associates, proving that, *in addition to* the anti beriberi factor, vitamin B contains a pellagra preventive factor, the United States Public Health Service, without admitting its error in announcing that "*the* cause of pellagra is an unbalanced diet deficient in certain amino acids," announced emphatically that deficiency of vitamin G is the cause of pellagra This announcement was given widespread publicity, and Goldberger's second theory was accepted by the newspapers of the nation and by a large part of the medical profession, though probably a majority of the physicians who have had experience dealing with endemic pellagra did not

accept the theory that deficiency of the pellagra preventive factor in vitamin B is the sole cause of pellagra. Many agreed, however, that a vitamin deficiency diet is a factor in the etiology of pellagra.

It is interesting to note that many of the leading experts on nutrition in the United States did not accept the single vitamin deficiency theory in the etiology of pellagra. As late as 1928 Goldberger's theory of a deficiency in the pellagra preventive factor in vitamin B was not accepted by the Committee on Nutrition of the American Public Health Association, of which Henry C. Sherman was chairman.

All observers agree that the food is an important element in the production and cure of pellagra, but formerly many dissented from the idea that a deficiency of Goldberger's pellagra preventive factor in vitamin B is the *fons et origo* in its etiology. J. S. McLester, as late as 1934, summarized the divided opinion regarding the etiology of pellagra when he said: "Goldberger's final conclusion that pellagra is due to a specific dietary fault, *lack of vitamin G, is now generally accepted the country over,* except, it should be noted, in those areas in which the disease occurs with greatest frequency."

McLester at that time suggested that pellagra may be "the expression of a multiple food deficiency." He now believes that nicotinic acid deficiency is the essential cause of pellagra, but that other vitamin deficiencies are present in a large proportion of the cases.

Partlow's Views.—W. D. Partlow, Superintendent of the Alabama Hospitals for the Insane, has had as large an experience with human pellagra as any physician in the United States. When the first outbreak of pellagra reported in the United States occurred in the Alabama Hospital for Insane Negroes at Mount Vernon in 1906, Partlow was resident physician in the Bryce Hospital for Insane Whites in Alabama, at Tuscaloosa. A number of cases of pellagra were reported by Jas. T. Searcy in 1907. Partlow therefore has been studying pellagra for thirty-four years. He has been a careful student of the diseases associated with insanity and is a man of judicial temperament. He thinks independently and expresses his views only after mature study and careful consideration. The opinion of such

physician is worthy of careful study by those who are interested in the etiology of pellagra

Partlow, who has been a member of the State Board of Health of Alabama for many years and therefore is interested in preventive medicine, in a communication to the *Journal of the Medical Association of the State of Alabama* in 1938, protested vigorously against the statement made in a Bulletin of the United States Public Health Service that "pellagra is strictly a dietary deficiency disease due to diets containing inadequate quantities of the pellagra preventive factor in vitamin B" Partlow expressed what was in the minds of many physicians who have had large experiences in treating human pellagra when he said

In a recent quotation made by the State Health Department from a United States Public Health Bulletin and circulated among the physicians of the state appears the following

Pellagra is strictly a dietary disease and is caused by an inadequate supply of an essential food element which belongs to the class of accessory food principles known as vitamins Pellagra results from a diet which does not permit a sufficient supply of anti pellagric vitamins or vitamin G'

"For reasons to be given below, I am compelled to take issue with the prudence and propriety of the above definite and positive statement I maintain that up until the present at least the proper position to be maintained is that pellagra is a disease of unknown cause The late Dr Goldberger did not, nor has anyone else proven pellagra to be due to a dietary deficiency cause Had the same experiments been performed in connection with tuberculosis the same results probably would have obtained If two groups of persons had been subjected to a known infected residence or ward with tuberculosis one group being given ample, well balanced nutritious diet and the other given a limited unbalanced or starvation diet the result expected would have been that many on limited or starvation diet would have developed tuberculosis while scarcely one if a single one being fed a wholesome diet would have taken the disease just as was the case with the pellagra experiment Malnutrition or diet deficiency no doubt predisposes to tuberculosis pellagra or any of the other diseases to which vital resistance is the defense

On the other hand the history of pellagra as a disease and the course it pursues in the individual cases all argues in favor of some obscure or unknown specific cause of an infectious or bacterial nature

'The adherents to the dietary theory as a cause do not produce any evidence or proof which undertakes to explain away or satisfactorily reconcile four outstanding contradictory facts as follows

First *The Sudden Appearance of Pellagra in Almost Epidemic Form Argues for Specific Cause As Against Dietary Cause*—We know

there had been only rarely a case in this country before 1902, only a sporadic case being reported here and there in the literature It appeared all over the southeast, spreading between foci until 1905 and 1906 it became prevalent There was no sudden change, diminution or restriction of dietary throughout the general population of our southeastern country coming on suddenly and at once as did the appearance of pellagra in this territory

"Second *Geography and Climate*—There is no justification of the assumption that dietary became restricted only in the southern and southeastern country about the time of the advent of pellagra, and from that time until now as against the common knowledge that the poor in the slums of eastern and northern cities, and certainly the poor in as many instances of rural population of the east and north were on limited or deficient diet at the same time, whereas, in 1905, 1906 and 1907 when pellagra was most prevalent and most virulent south of the Potomac River (southeastern states and including only two states north of the Ohio, and only two or three states of the south lying west of the Mississippi), while there were no cases of pellagra to be found in the north and east At the time pellagra was most prevalent the writer visited institutions of Georgia, South Carolina, St Elizabeths at Washington and New York institutions being already familiar with conditions here in Alabama A very high per cent of the population of the Georgia and South Carolina institutions both white and colored had pellagra At that time no case had been seen in St Elizabeths and no case in the New York Institutions The dietary of all of the institutions was practically the same About fifty per cent of the cases in the institutions that had pellagra were brought in with the condition and about half of the cases had developed in the institutions arguing against the possible assumption that institution's defective dietary might have been a factor I maintain that if pellagra was due solely to dietary cause there would have been as many cases in the north and east as there were in the south and southeast, all dietary factors in the institutions being the same, and the diet of the contributing general populations not differing materially

Third *Influence of Seasons*—If pellagra was due solely to dietary cause we should have more cases appearing in the winter than in the spring and summer while vegetables and fruits are in season whereas we know that pellagra is a spring and summer disease If deficient diet was the sole cause we should have the condition more prevalent in winter than in summer We know new cases do not appear after the first heavy frosts or freezes, as does malaria or yellow fever

"Fourth *Severity and Mortality Rate Materially Reduced*—There is every evidence that the disease has become attenuated as is the history with known infectious diseases being extremely fatal and virulent in the early history of pellagra in this country (1900 and to 1910), and either from acquired resistance of the population or from attenuation of infection becoming less virulent as the years pass We know in the beginning that practically every person who showed the characteristic symptoms of pellagra within the first few years after the sudden advent

of the disease would die The rate of mortality has gradually from year to year reduced until now only a relatively small per cent of the pellagrins die with the disease All doctors know that this alteration and reduction of mortality rate cannot be attributed to treatment or management but has come gradually from some unknown diminution of virulence factor

'There are other outstanding evident facts that are not in accord with the dietary theory as a cause I maintain that the assumption of diet as a sole cause does not explain away the facts outlined above nor does it line up with them '

Since the above article was published Partlow and his associates in the Bryce Hospital for Insane Whites in Alabama at Tuscaloosa, collaborating with Spies, have used nicotinic acid in the treatment of many cases of pellagra He is convinced in the efficacy of nicotinic acid therapy in pellagra, but he believes that the facts which he brought out in 1938 are still facts, and that other factors in addition to a deficiency of nicotinic acid in foods play a part in the production of pellagra

The Relation of Avitaminosis to Pellagra—McCollum in the first edition of his *The Newer Knowledge of Nutrition* in 1918 suggested that vitamin deficiency may be a predisposing factor in many infections and that a diet deficient in vitamins may thus act as an underlying cause of pellagra McCarrison, in 1920, proved that a diet devoid of all the vitamins predisposes to many infections of the gastrointestinal tract

McCarrison a British Army Surgeon, stationed in a remote region of the Himalayas, observed that the natives rarely had gastrointestinal and other abdominal infections, which accounted for about 25 per cent of the hospital admissions in England After studying the habits and mode of life, including the diet, of the ignorant natives, he concluded that what he called their "natural" diet, i e , bread made from whole grain cereals, milk, leafy vegetables and fruit, articles of food rich in vitamins, protected them against the infections which are so frequently found in civilized man, who consumes largely devitaminized foods McCarrison experimented on monkeys, feeding them on autoclaved rice, devoid of all vitamins, and found that they developed enterocolitis, ulcer of the duodenum, and gall bladder infections, whereas monkeys in an adjoining cage fed on the natural diet of the natives did not develop either acute or chronic gastrointestinal infections

McCarrison found that the mucosa of the intestines of monkeys fed on autoclaved rice had lost their resistance to infections, and in one of his illustrations he showed a photomicrograph of a section of the intestines in which bacteria could be seen in the blood vessels He did not apply his findings to the genesis of pellagra (apparently the natives of Himalaya do not have pellagra) but in 1925, in an address on pellagra at the International Conference on Health Conditions in Tropical America, at Kingston, Jamaica, I suggested that McCarrison's studies seemed to indicate that the role of avitaminosis in predisposing to infections, may thus be a primary factor in the production of pellagra

At that time I did not visualize liver damage, secondary to intestinal infections, as a factor in pellagra, but in 1927 I suggested that liver pathology, with resulting impaired function of that important organ, may be a factor in the etiology of pernicious anemia and pellagra More recent investigations by biochemists and physiologists indicate that the liver stores up all the vitamins, and that an intact, properly functioning, liver is necessary for the utilization of vitamins, B complex in particular It, therefore, seems that the first effect of avitaminosis in the production of pellagra, is to lower resistance of the stomach and intestines to invasion by pathogenic bacteria, and that liver damage, from toxins formed in the gastrointestinal tract secondary to avitaminosis, is a predisposing factor in producing nicotinic acid deficiency

Multiple Vitamin Deficiencies in Pellagra—A notable contribution bearing on avitaminosis as a predisposing cause of infections, and their possible relation to pellagra, was made by Smith, Persons, and Harvey of Duke University in 1937 It will be recalled that in 1917 Chittenden and Underhill and Mendel produced blacktongue in dogs by depriving them of vitamin A, and cured them by the use of carotene Goldberger and Lillie, in 1926, also produced canine blacktongue by feeding them a diet deficient in the pellagra preventive factor in vitamin B Smith and his associates repeated the experiments both of Underhill and Mendel, Goldberger and Lillie with the results that the dogs fed on diets deficient in vitamin A and those fed on the pellagra producing diet developed blacktongue

with the same clinical and bacteriologic findings They concluded, however, that blacktongue in dogs due to deficiency of the pellagra preventive factor was the analogue of human pellagra Of particular importance was *the fact that Smith and his* associates found enormous numbers of fusospirochetal organisms in the oral lesions of dogs fed on diets deficient both in vitamin A and the pellagra preventive factor It would seem if vitamin deficiency predisposes to oral infections, that McCarrison may have been right in his opinion that vitamin deficiency may be the primary factor in gastrointestinal infections

McCollum in the last edition of *The Newer Knowledge of Nutrition,* in discussing the findings of Smith and his associates, said

' This observation is of additional outstanding importance since it makes clear the fact that microbal agencies which in the well individuals are not able to establish themselves upon mucous surfaces and become a menace to health may easily do so when the vitality is lowered through malnutrition In this case the overgrowth of fusospirochetal organisms occurred equally menacingly in two distinct deficiency states "

While nicotinic acid deficiency may be accepted as the exciting cause, or the essential factor, in the production of pellagra, it is questionable if any case exists without varying degrees *of deficiencies of other vitamins Deficiencies of vitamin* A, thiamin, ascorbic (cevitamic) acid, riboflavin and other factors of the B complex, and other nutrients essential to health and life are known to exist in a large proportion of the individuals whose cases have been diagnosed as pellagra Vitamin deficiencies, other than nicotinic acid may be predisposing causes of pellagra, or, they may be complicating conditions In other words, the individual who is in a lowered state of vitality from a deficiency of vitamin A, and, or, thiamin riboflavin and other factors of the B complex, ascorbic acid, vitamin D and other protective nutrients, is prone to develop a deficiency of nicotinic acid to the extent that pellagra is the sequence It also is true that varying degrees of other vitamin deficiency states notably polyneuritic (beriberi) and scurvy, are important, and not infrequent, complications of pellagra

The viewpoint that all there is to pellagra is a deficiency of the pellagra preventive (P P) factor (nicotinic acid) in vitamin B in the food of the victim, and all that is necessary to cure him is to prescribe yeast, or nicotinic acid, is untenable Therefore, in the effort to find the cause and remove it in any given case of pellagra the predisposing factors and the complicating conditions should be considered

The concept of a multiple vitamin deficiency, not necessarily as the cause of pellagra, but as a factor in the disease, is believed in by many clinicians and laboratory investigators Mellanby believes that vitamin A deficiency plus an inadequate intake of the pellagra preventive factor are essential for the production of pellagra Roussel believes that vitamin C (cevitamic acid) deficiency is always a factor in pellagra Ruffin Sydenstricker, Spies, J S McLester, and many others are impressed with multiple vitamin deficiencies in pellagra

The Relation of Infections to Avitaminosis—The viewpoint that pellagra is both a nutritional and an infectious disease has been held by many In 1928 the Committee on Nutritional Problems of the American Public Health Association, of which E L Sherman was Chairman, in discussing the etiology of pellagra said "Tuberculosis is also a disease in which both infection and nutrition are involved, though here still other factors are known to be involved also and the case seems distinctly different because the infections agent is well known It is possible, however, that if we knew both cases better the comparison between these two diseases might seem much more natural"

Many believe that a deficiency of vitamin A predisposes to infections of all kinds, though it cannot be said there is proof that such is a fact Mellanby is impressed with the relation of vitamin A to infections and advises its use in the prophylaxis and treatment of septicemia and infectious diseases

McCollum says further ' Dietary intake alone of the vitamin is not sufficient to insure its utilization Reports of secondary cases of avitaminosis A are appearing in the literature, which are due to deficient absorption of this substance Among this group are cases of gastrointestinal and hepatic disease, and of severe [illegible]ections '

If a deficiency of vitamin A in diets predisposes to gastro intestinal and hepatic diseases, it can be seen readily that gastric and hepatic insufficiency may be followed by nicotinic acid deficiency The sequence of an inadequate supply of nicotinic acid for the needs of the human body, being followed by secondary gastrointestinal infections, and hepatic insufficiency may be predicated

That varying degrees of a deficiency of the other factors in the vitamin B complex exist in pellagra cannot be doubted It must be remembered that nicotinic acid is a fraction of vitamin B A diet so deficient in nicotinic acid that pellagra is produced would surely be deficient likewise in thiamin and riboflavin, though not necessarily to the extent of producing beriberi and or, the riboflavin syndrome, denominated by Sebrell as ariboflavinosis

McCollum's Comments—McCollum cites Castle and Rhoade's report of a study of 75 cases of chronic ulcerative colitis as showing "evidence of nutritional deficiency in 63 per cent Deficiency multiple not only in vitamins but also in protein and essential organic elements" It will be recalled that a number of cases of pellagra have been reported as secondary to ulcerative colitis McCollum also cites the conclusion of Borsook and his associates who found from a study of 237 cases of chronic gastrointestinal malfunction that there exists "a widespread partial B complex deficiency and that most people require for normal gastrointestinal function several times the minimum amounts of water soluble vitamins required to prevent severe deficiency diseases such as beriberi and pellagra"

McCollum in 1918 expressed the opinion that vitamin B deficiency was widespread in the United States and that many cases of unclassified functional nervous diseases are due to this cause He also suggested the existence of many borderline cases of beriberi, as a result of the changed eating habits of all classes of people He considered the extensive use of white flour and white meal bread, polished white rice and other de vitaminized cereals, white sugar and other cane sugar products to the exclusion of vegetables and fruits, as a menace to the health of a considerable portion of the people in the United

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States McCollum did not believe at that time that food deficiency was the sole cause of pellagra He now accepts nicotinic acid deficiency as the essential factor in the production of the disease

Spies, in many papers, has stressed the fact that multiple vitamin deficiencies, particularly thiamin avitaminosis, are present in a very large proportion of cases of pellagra, and that in the treatment of pellagra, thiamin and riboflavin should be used along with nicotinic acid when indicated, and that full well balanced diets, rich in all the vitamins, should be continued long after all the symptoms of pellagra have subsided

Other Vitamin Deficiencies in Pellagra—The investigations of Spies and Aring on the effect of thiamin on the peripheral neuritis of pellagra indicate that the nervous manifestations of pellagra may be due to a deficiency of the antineuritic factor in vitamin B_1

Spies and Aring found that the intravenous injection of crystalline vitamin B_1 relieved the neuritis of pellagra promptly and that nicotinic acid promptly cleared up the mouth and *gastrointestinal symptoms* *In commenting on their results* in the use of thiamin (crystalline vitamin B_1) in pellagra in which peripheral neuritis was a troublesome symptom, Spies and Aring concluded that "vitamin B_1 does not cure the glossitis and the stomatitis of pellagra, and nicotinic acid which does cure these symptoms will not cure the peripheral neuritis"

Many foreign investigators in pellagra accept the pellagra preventive factor in vitamin B as only one of the factors involved in the etiology of pellagra As mentioned, E Mellanby produced pathologic posterior and lateral cord changes in rabbits by feeding them on rich cereal diet poor in vitamin A Mellanby considers that while the skin lesions of pellagra are due to vitamin B deficiency the nervous complications are due to vitamin A deficiency

Sclare points out the similarity between symptoms of hypoadrenalinism and pellagra and questions the specific value of the pellagra-preventive factor in vitamin B in pellagra He describes a case showing pellagra as a terminal manifestation of hypoadrenalinism, and this case shows that many of the

features characteristic of functional hypoadrenalinism in pellagra, and secondary pellagra, strongly indicate that these conditions have etiologic factors in common He suggests that two etiologic factors in pellagra are (1) primary hypoadrenalinism and (2) inadequate augmentation of adrenal functioning by diets deficient in vitamins

It is interesting to note that Sebrell and Draft in a recent address before the American Academy of Pediatrics (Washington *Star*, April 4, 1940) mentioned that a deficiency of pentothenic acid, one of the factors in vitamin B, in the diets of rats results in degeneration of the cortex of the adrenal glands of the animals Since a deficiency of cortin, the internal secretion of the adrenal cortex, is the recognized cause of Addison's disease, it seems possible that in some cases of pellagra there is a deficiency of nicotinic acid and pentothenic acid If so in such cases, in addition to the pellagra syndrome, there should be manifestations of Addison's disease I can recall cases of pellagra in which pigmentation of the face, neck, and body resembled closely the appearance of the skin in Addison's disease

Ellinger, Hassan, and Taha in recent investigations on pellagra in Egypt while accepting the "vitamin G deficiency as a cause consider that another factor is present" They found that "parasitic infection in the gastrointestinal tract was almost invariable in pellagrins and much less frequent in non pellagrous population" They believe that "pellagra in Egypt results from two concomitant but independent factors Malabsorption due to parasitic infection of the intestines and malnutrition due to diets insufficient in vitamin B complex"

Biggam and Ghalioungui report a marked decrease in pellagra in Egypt, in one hospital from 129 cases in 1920 to 63 cases in 1930 They found that in 24 of 26 cases there were parasitic infestations "This high helminthic infestation rate for pellagrous patients compared with the general infestation rate of the population in Egypt suggests that infestation may play a part in the production of the disease and accounts for its occurrence in only certain members of a family, all of whom are on the same deficient, ill balanced diet"

Sydenstricker's Gastric Intrinsic Factor—Sydenstricker and Thomas in discussing a possible gastric intrinsic factor in the

etiology of pellagra premised their study of a series of patients treated with normal gastric juice as follows

"The definite etiology of pellagra remains obscure No theory yet advanced holds in all instances or fully explains all the phenomena of the syndrome Particularly is this true of its tendency to seasonal occurrence and relapse, periodic increase and decrease and occasional epidemic prevalence Yet certain factors assume importance in all epidemics and in all considerable series of cases Poor diet with avitaminosis intoxication, particularly chronic alcoholism infection and exposure to sunlight are prominent in varying frequency in all group histories Each and all can be ruled out in many cases This lack of consistency in presumptive etiology has been confusing and has led to empiricism in therapy and perhaps to neglect of critical observation The various lesions of the disease have been a pathologic problem The dermatitis is distinctive the glossitis with papillary atrophy and the atrophic state of the gastrointestinal mucosa have much in common with pernicious anemia and sprue The frequent fatty degeneration of the liver is of possible significance"

The results obtained by Sydenstricker and Thomas in the treatment of 6 cases of severe pellagra while continuing a diet poor in the pellagra preventive factor in vitamin B (nicotinic acid) was comparable to those obtained in severe cases treated with yeast They describe their study as follows

'A small group of patients with severe pellagra, growing worse on the test diet, were subjected to the experiment Of six patients who had no treatment other than gastric juice, five recovered quite promptly, one died of an acute intercurrent infection Others were given gastric juice in conjunction with other therapy but are not considered here Those patients who secured remission were kept on the test diet for periods ranging from three weeks to three months without relapse three are known to be well eighteen months to three years later One relapsed a year after treatment and recovered again under different therapy, one had been lost from observation This experiment led us to believe that normal gastric juice does contain a substance which is essential to the cure of pellagra and that the prolonged remissions with failure to relapse on test diet indicate the storage of an essential curative substance in the patient's body If the analogy to pernicious anemia and sprue but more complex than either holds the essential curative substance is produced by the interaction of an intrinsic factor present in normal gastric juice (and perhaps in the gastric juice and stomach of animals) with certain components of the vitamin B complex This essential substance is probably stored in the liver Absence of the intrinsic factor and exhaustion of the stored essential substance result in the symptom complex of pellagra"

They concluded that "no current theory of the etiology of pellagra satisfied all requirements The hypothesis is advanced

of an intrinsic deficiency, analogous to but distinct from that of pernicious anemia and sprue"

Petri, Svend, Wanscher, and Teglbjaerge believe with Sydenstricker that there is an antipellagra intrinsic factor in the gastric mucosa in addition to the pellagra preventive substance in food Their careful studies were based upon the premises that many patients with pellagra do not recover when on full diets and yeast Other patients recover spontaneously on a pellagra productive diet Then "the idea of an antipellagra intrinsic factor in the gastric mucosa emerged an analogy to the antianemic intrinsic factor in the liver"

Petri and his associates cured severe cases of blacktongue in dogs by the use of human gastric juice Petri gives Spies credit for being "the first in 1934 to try stomach preparations in cases of pellagra which did not respond satisfactorily to yeast He (Spies) observed good results with ventriculin (desiccated, defatted and pulverized hog stomachs)"

Recent studies by Sydenstricker, outlined in his chapter in this book, seem to show that a gastric intrinsic factor exists in pellagra as surely as there is such a factor in the genesis of pernicious anemia

The End of the Quest for the Essential Factor in the Etiology of Pellagra—The quest for the essential factor in the genesis of pellagra had a dramatic ending Stages were set in hospitals in Birmingham Alabama, Durham, North Carolina, Augusta Georgia, Cincinnati, Ohio, and Indianapolis Indiana to play the final act following Elvehjem's "Rin Tin Tin" scene laid in the experimental laboratories in the Department of Biochemistry of the University of Wisconsin The actors in the last scene had been trained to perform their parts by years of clinical research in pellagra, and the curtain went down on the final act of the drama, 'The Quest for the Cause of Pellagra," leaving interested physicians impressed with the idea that they had witnessed another miracle of modern scientific research

That nicotinic acid is a specific in the treatment of pellagra was proved in a few weeks by the dramatic recoveries of hundreds of cases treated by Ruffin and Smith in Durham, North Carolina, Spies, Cooper Clark, Blankenhorn, Aring Gelperin,

and Bean in Cincinnati, Spies, Chinn, and J B McLester in Birmingham, Sydenstricker and associates in Augusta, Georgia, Fouts and his associates in Indianapolis, and many other clinicians All observers agree that the oral and gastrointestinal symptoms of pellagra begin to improve within twenty four hours after the patient is given adequate doses of nicotinic acid Spies reports that the "acute mental symptoms varying from slight confusion to delirium and mania respond dramatically, in most cases, over night" He also said "The dermal lesions improved rapidly under the use of nicotinic acid except where the continuity of the skin was broken and the lesions were moist, ulcerated, dry or pigmented" Spies also reported that "porphyrinuria in pellagrins cleared up within one or two days after the use of large doses of nicotinic acid"

Ruffin and Smith reported a large series of cases of pellagra treated with nicotinic acid They are convinced of the curative effect of nicotinic acid in the treatment of pellagra but warn that "other deficiencies may co exist, which, if uncorrected, will interfere seriously with the curative effects of nicotinic acid" They add "The evidence seems clear, however, that the cardinal symptoms of active pellagra, namely, the glossitis, anorexia, diarrhea and dementia, subside promptly, and in many cases dramatically, after the administration of nicotinic acid alone"

Sydenstricker, in reporting 250 cases of pellagra treated with nicotinic acid, said "The specificity of this vitamin in the cure of stomatitis, glossitis, and psychic disorders cannot be over emphasized" Sydenstricker, who is impressed with multiple deficiencies in pellagra, adds "Occasional patients have not responded to nicotinic acid but have been cured by liver extracts given intravenously" Sydenstricker also reported "A group of stuporous patients showing no definite signs of pellagra but who had fiery red tongues suggestive of vitamin deficiency responded to nicotinic acid by regaining consciousness"

Spies and his associates gave nicotinic acid as a prophylactic to a large number of known pellagrins with complete success in preventing recurrences while on pellagra productive diets, so that its use in the prevention of pellagra has been estab

lished If nicotinic acid will cure the manifestations of pellagra, and if it will prevent the disease it must be the factor essential for its production

That nicotinic acid is one of the factors in vitamin B was shown by Funk, who isolated it from yeast in 1912, but it was Goldberger and his associates who proved the existence of a pellagra preventive factor in vitamin B, and to them must be given a large share of the glory for the achievement of solving the problem of the essential cause of pellagra

SECTION III

ETIOLOGY AND PATHOLOGY

CHAPTER X

CONDITIONS AND DISEASES WHICH INCREASE SUSCEPTIBILITY TO PELLAGRA

Age.—Pellagra, like tuberculosis, takes its toll largely from persons in the productive period of life. Katherine Dodd, in the chapter on "Pellagra in Childhood," shows that while the disease is relatively infrequent in childhood, it occurs even in infancy. Stewart Roberts reported a case in a woman at the age of one hundred and two years.

Deaderick and Thompson cite the statistics of Merck on the age incidence in 4,863 cases. Merck's table of ages is as follows:

From 0 to 5 years	46 cases or 0.9 per cent
From 5 to 15 years	406 cases or 8.3 per cent
From 15 to 30 years	715 cases or 14.7 per cent
From 30 to 40 years	919 cases or 19.0 per cent
From 40 to 50 years	1,017 cases or 21.0 per cent
From 50 to 60 years	868 cases or 18.7 per cent
From 60 to 70 years	638 cases or 13.1 per cent
Over 70 years	228 cases or 4.6 per cent

Sex.—The preponderance of pellagra in females has been commented upon by many. In Searcy's cases in the first outbreak at Mount Vernon, Alabama, there were 80 females and 8 males. In 1916 Deaderick and Thompson compiled reports of 21,279 cases of endemic pellagra in the United States, according to sex; 6,039 were males and 15,265 were females.

In alcoholic pellagra the males predominate or at least have predominated. If drinking among women increases, a larger proportion of cases of pellagra in females may be expected. A well known clinician mentioned the case of a wealthy man and his wife who, after several years of habitual drinking, both developed pellagra.

Season—Seasonable variations in the incidence of pellagra are pronounced, apparently depending upon the climate of the countries in which the disease is endemic. Deaderick and Thompson in *Endemic Diseases in the South,* state that pellagra is most frequent in the months of April, May, and June, the onset appearing earlier in the countries lying farther south. They say that in Florida more cases originate in the early spring months than in states farther north. In Italy the majority of first cases are said to occur from the middle of March to the middle of May and the disease appears somewhat earlier in the central provinces than in the northern ones. Sandwith states that "in examining 300 patients in Egypt two thirds of them stated that their skin lesions were first seen during the months of January and February."

Deaderick and Thompson prepared a table compiled from 413 cases collected by Grimm, Walker, Tucker and Mizzell which shows the number in which the first symptoms occurred according to months.

MONTH	TOTAL	MONTH	TOTAL
January	8	July	57
February	16	August	30
March	47	September	13
April	62	October	18
May	86	November	8
June	88	December	5
			4 8

It appears from this table that beginning in July there is a pronounced monthly drop in the number of cases until in December when only 5 of the 438 cases occurred. It will be noted that in August, the hottest month of the year, there are only 30 cases as compared with 62 in April and 86 and 88 in May and June.

Pellagra Largely a Rural Disease—Observers in the endemic areas of pellagra agree that it is largely a rural disease. The late Isadore Dyer reiterated on many occasions that he had never seen a case that originated in the sewered section of a city. Stewart Roberts, one of the early students of pellagra, said in his book "Pellagra stops at the city gates." Deaderick and Thompson in their book, *Endemic Diseases of the South* considered pellagra essentially a rural disease.

Wood found two types of pellagra in North Carolina Many of the large group were found among rural inhabitants, or in city dwellers who had moved from the country or had visited relatives in rural localities Wood found a few cases in bona fide city dwellers, but they were among the very old or in persons who were debilitated from other diseases and conditions

More recently many cases have been found among alcoholics in the cities, particularly in sections of the country in which pellagra is not endemic Many cases of what is called "secondary pellagra" occur in persons living in cities who are in a lowered state of vitality from chronic diseases, particularly malignant conditions of the stomach, intestines, and rectum

That endemic pellagra has continued as largely a rural disease in the South is admitted by most observers

Heredity—While Lombroso did not believe that heredity played any part in the production of pellagra, many of the Italian pellagrologists were convinced that pellagra is a hereditary disease like syphilis H F Harris believed in the heredity of pellagra, and in his book he cites Italian authorities on pellagra upholding his position

The consensus of opinion in the United States is that pellagra is not hereditary I have had little experience in treating pellagra in children, since my practice has been confined to internal diseases in adults, with an occasional adolescent patient, but I have seen no evidence of heredity in any case of pellagra It seems probable, however, that children of pellagrous parents, like children of tuberculous parents, are more susceptible to the disease than offspring of healthy parents because of inherited lowered resistance, and because they live in an environment in which the disease occurs

No cases of fetal pellagra have been reported, but cases have been observed in infants a few weeks old No case of pellagra has been reported in a newborn baby

Pregnancy—Pregnant women in localities in which pellagra is endemic are prone to develop pellagra Likewise, pregnancy in a pellagrin is often followed by serious consequences, just as pregnancy in a tuberculous woman may light up a latent pulmonary focus Griffith, of Columbia, South Carolina, said that pregnancy may bring to light latent pellagra

It can hardly be said that pregnancy in a normal, healthy woman is a predisposing cause of pellagra, *nevertheless, no* doubt in pellagrous districts many women would never develop the disease had they not had the hazard of pregnancy

Lactation—Pellagra has been observed in women during lactation only in pellagrous districts, but it has never been found in a nursing woman in localities in which pellagra is not endemic It is probable that pellagrin mothers are more prone to develop active symptoms while debilitated from nursing and caring for their children, but normal lactation in a healthy woman cannot be considered a predisposing cause of pellagra

The late William Krauss, of Memphis, related interesting observations on pellagra in two nursing mothers Krauss observed a nursing infant who had contracted pellagra at the age of six months, and was getting no nourishment except from a healthy mother Another child showed precisely the opposite state of affairs The mother had suffered from a virulent form of pellagra, and during four weeks had nursed her infant and the infant was in perfect health

Syphilis—Babes considered syphilis as an important predisposing cause of pellagra and cited many cases of pellagra secondary to syphilis He also pointed out that in southern Europe, countries in which pellagra prevails, a large proportion *of the inhabitants have syphilis*

J S Turberville, of Century, Florida, who reported the first cases of pellagra in Florida in 1908, in discussing the relation of syphilis to pellagra, brought out interesting parallel points of similarity between pellagra and syphilis, which make clear that pellagra occurs frequently in neglected syphilis

Sydenstricker and Armstrong, in a study of 440 cases of endemic pellagra at the University of Georgia Hospital, Augusta, Georgia, found that 57 had syphilis They did not mention whether the pellagrins had syphilis before they developed pellagra, but presumably syphilis was the primary disease in most of them

Certainly syphilis and pellagra, while having many points of resemblance, are unrelated diseases, but it is equally patent that the syphilitic patient who is in a lowered state of vitality

from his primary malady is more likely to develop pellagra than a normal healthy person who is not infected with the *Treponema pallidum*

Malaria —Wood reported in 1904 a case of quartan malaria in which the patient had symptoms of pellagra Malaria prevails almost everywhere that pellagra is endemic, and while many have considered it possible that mosquitoes are the vectors for both, no one has suggested that malaria bears any other relationship to pellagra than as a predisposing factor Pellagra and malaria have been found so often in the same individuals that one must be a predisposing cause of the other Certainly the person infected with malaria is more likely to develop pellagra than one whose vitality has not been sapped by chronic disease There can be no doubt but that pellagra is often secondary to malaria

Infections and Deficiency Diseases —A person in a lowered state of resistance from many infectious diseases may develop pellagra It has been known to follow typhoid fever in a number of cases Ross Snyder cited H W Rice as having reported outbreaks of pellagra in two orphanages following epidemics of measles and whooping cough

If pellagra is a deficiency disease analogous to polyneuritis, it would seem that the same predisposing causes would apply to both conditions Cobb and Coggershall list the principal causes of polyneuritis as 13 virus diseases, including measles, smallpox, poliomyelitis, encephalitis, 20 bacteriotoxic diseases, and about the same number of diseases due to "deficiency or metabolic changes, among which they list pernicious anemia sprue, and diabetes "

Intestinal Protozoa —*Endamoeba histolytica, Giardia lamblia,* and other protozoa, the habitat of which is in the intestinal tract, have been found so frequently in the feces of pellagrins that many believe they have a relationship to pellagra

So many cases of amebiasis have no manifestations of pellagra that it could not be possible for the *Endamoeba histolytica* to be the primary cause of the disease On the other hand, pathogenic protozoa are found so frequently in pellagrins there can be no doubt but that amebiasis is a predisposing cause of

pellagra The relation of amebiasis and *Giardia lamblia* infestations to pellagra is discussed in the chapter on "Infectious Theories"

Uncinariasis—Pellagra and hookworm disease have been found together so constantly in regions in which both are endemic that a possible relationship has been suggested No doubt uncinariasis predisposes to pellagra, as the anemic undernourished pellagrin is a victim of tuberculosis and many other chronic diseases

Alcoholism—Alcoholic pellagra is discussed in another chapter Rutledge no doubt was right when he said in substance that the alcoholic is a potential candidate for pellagra Certainly alcoholism is a potent predisposing cause of pellagra

Tuberculosis—Tuberculosis is frequently associated with pellagra, perhaps for the reason that malnutrition is a predisposing cause of both diseases B E M Green, of the Georgia State Sanitarium, reported 25 cases of pulmonary tuberculosis in 131 cases of pellagra Sydenstricker and Thomas reported 18 cases of tuberculosis in their 440 cases No doubt tuberculosis is one of the predisposing causes of pellagra, but in many cases the pellagra and tuberculosis may develop concurrently, and tuberculosis may be a sequel of, and the terminal stage in, pellagra

Arteriosclerosis—Pellagra may be the terminal condition in senility, and no doubt arteriosclerosis is one of the many predisposing causes of the disease Green found arteriosclerosis as a complication in 10 of his 131 cases of pellagra, while Sydenstricker and Thomas found it in only 10 of their 440 cases

Diabetes Mellitus—Severe diabetes mellitus no doubt is a predisposing cause of pellagra, but in the approximately 1 500 patients with diabetes mellitus whom I have treated, there has been only one who had pellagra Many of these diabetic patients were advanced cases when they came for treatment and some were very much emaciated In recalling some of the pitiful cases of advanced diabetes, particularly in children who were anemic, prostrated and reduced to skin and bones from malnutrition when they came for treatment, it is surprising that more of them did not develop pellagra Certainly avita

minosis exists in many cases of diabetes, particularly in the neuritides, which Spies has shown is due to a deficiency of thiamin (B_1) in a number of cases No doubt diabetic patients who have neuritis likewise suffer from nicotinic acid deficiency but not to the extent of producing pellagra

Secondary Pellagra—Chronic diseases of the gastrointestinal tract are frequent precursors of pellagra Malignant diseases, carcinomas usually, from the mouth to the rectum may produce the nicotinic acid deficiency essential in the production of cancer Acute pellagra is a not infrequent complication following colostomies and resections of the colon in cancers of the colon No doubt the secondary avitaminosis in carcinoma of the colon is one of the reasons for the high mortality in operating upon victims of abdominal malignancies

Neglected cases of ulcer of the stomach and duodenum with cicatricial stenosis of the pylorus and gastrectasis may be primary factors in the production of pellagra So many cases of secondary pellagra have been reported in cases of ulcerative colitis that a victim of that dreadful disease may be considered as a potential pellagrin

Immunity and Susceptibility—There is no evidence to show that one attack of pellagra confers immunity from other attacks, but on the contrary there is the tendency to recurring attacks, recrudescences from year to year Cases have been recorded in which pellagrins have had no symptoms in several years and then develop attacks typical of pellagra Apparently one attack of pellagra makes the individual more susceptible to all the manifestations of pellagra than if he had not been a previous victim of the disease

Certain individuals seem to be more susceptible to pellagra than others There may be one member of the family who has pellagra while others in the same house eating the *same food*, and living under identical hygienic conditions are perfectly well

Race—Apparently there is no racial immunity to pellagra A larger proportion of negroes than whites have pellagra in the South, and the death rates are inordinately high among the negroes for the same reason that tuberculosis, syphilis, and all other communicable diseases prevail and are more fatal among the negroes than in the white population, both in the

South and in the North Advocates of the food deficiency theory ascribe the relatively higher morbidity and higher mortality of pellagra among the negroes of the South to poverty and insufficient food, while those who believed in soil pollution, and possible insect transmission, pointed to the fact that negroes have a larger incidence of amebiasis, typhoid fever, and other water and soil borne diseases than whites In many rural districts of the South in which pellagra prevails, the negro population outnumbers the white from five to ten to one

CHAPTER XI

THE EFFECTS OF SUNLIGHT IN THE GENESIS OF PELLAGRA

Since Frapolli recognized that pellagra was epidemic, or endemic, in Italy in 1771, it has been known that the sun's rays are deleterious to pellagrins Gherardini, cited by H F Harris, in 1792, produced skin lesions on various parts of the body of 10 *pellagrins by exposure to the sun's rays in the month of* June Gherardini also observed that with the recurrence of the skin lesions in pellagrins produced experimentally by exposure to the sun's rays, the other symptoms of pellagra reappeared He expressed the opinion that "insolation is not the cause of pellagra but that the skin lesions produced by exposure to the sun were only the local manifestations of a general malady"

In 1794 Strambio produced skin lesions repeatedly on various parts of the body of pellagrins by exposure to the sun, and he said that the lesions of pellagra occur only on the exposed part of the body, except on the palms of the hands Perround in 1856, concluded that the chemical rays, and not the luminous nor heat rays, caused the recurrence of skin lesions of pellagrins when exposed to the sun's rays H F Harris also cites Bouchard as having covered a part of the arm of a pellagrous patient with diachylon ointment, leaving a bare spot in the center When exposed to the sun's rays the unprotected part of the arm developed an erythema Bouchard expressed the opinion that it was the violet rays of the spectrum which caused the erythema in pellagrins

Bass on Sunlight and Pellagra—Bass, in 1910, was impressed with the observations of Raubitschek on the effects of sunlight on experimental animals In reporting his successful results in producing skin lesions in pellagrins by exposure to the direct rays of the sun, Bass said

"When we first began to recognize pellagra in New Orleans two years ago, on several occasions we placed patients in the sunshine with parts of the body exposed to see if skin lesions followed in from three



Fig 1—Note eruption on cheeks chin and neck the parts of the body exposed to sunlight (Courtesy of Ruffin and Smith Duke University School of Medicine)

to ten days, but it was soon observed that coincidentally with the development of the skin lesions, other symptoms already present grew worse, and symptoms that were absent at the beginning of the experiment often developed. In one instance insanity was much increased. In another severe diarrhea, stomatitis and salivation resulted. In others the diarrhea was increased and it was decided that the experiment was not justified."



Fig 2—Dermatitis of hands and arms extending to elbow. More pronounced on right hand and arm than on the left because of greater exposure to sun on that side. (Courtesy of Ruffin and Smith, Duke University School of Medicine.)

Suicide of Convalescent Pellagrin After Exposure to Sunlight.—The tragic ending of one of my pellagra patients in 1911 convinced me of the relation between sunlight and pellagra. The following is a brief report of that case.

Case Report.—A bank cashier about 40 years of age from Grove Hill, Alabama, had alimentary tract symptoms, including diarrhea, the typical skin lesions and the mental depression seen in severe cases of pellagra. Believing that the Weir Mitchell "rest cure" which includes isolation in a hospital, rest in bed, and forced and frequent feedings is the best treatment for pellagra, this pellagrin was kept in a hospital for a month. The stomatitis and glossitis were relieved in a few days, the diarrheas subsided, and the mental depression was followed by cheerfulness. When this patient, who by the way, was a prosperous educated gentleman, left the hospital he seemed perfectly well and was grateful for his recovery. His train arrived in Jackson, Alabama



Fig 3—Lesions on top of feet exposed to sun Note that there is no eruption on parts of feet and ankle covered by slippers (Courtesy of Ruffin and Smith Duke University School of Medicine)

about ten o'clock in the morning and he rode in an open buggy exposed to the hot sun to his home a distance of about twenty miles The day following the ride in the sun the dermatitis, diarrhea, and mental depression returned and a day or two later he committed suicide by slashing his throat from ear to ear with a razor I am firmly convinced that had this patient been cautioned sufficiently to keep out of the sun for the rest of that summer, he would be alive today, as are some other pellagrins who were treated at that time and later

Jobling's Studies —Jobling, former Professor of Pathology in Vanderbilt University, and his associates, Peterson and Arnold, made a notable contribution on the relation of sunlight to pellagra "Impressed with the possibility that pellagra may be due to a photodynamic substance produced by an organism located in the intestinal tract," they made studies on mice injected with an extract of cultures of a fluorescent fungus apparently belonging to the *Aspergillus glaucus repens* group, obtained from the feces of active and quiescent pellagra cases The mice showed no evidence of illness until after exposure to the sun when they developed symptoms analogous to pellagra, and many of them died

Jobling cited Meyer Betz as having sensitized himself to sunlight *with hematoporphyrin in 1913*, Meyer Betz found that after taking hematoporphyrin "exposure to sunlight caused marked edema and erythema of the exposed parts of the face, hands, neck, etc He remained hypersensitive for at least six weeks, though no traces of the sensitizing substance, hematoporphyrin, could be found after 72 hours "

Jobling cited Hausmann as having found hematoporphyrin in the urine in 1910, and he called attention to the fact that four European investigators suggested that this photodynamic substance when activated by the sun might cause pellagra

In view of recent studies on porphyrinuria in pellagra, Jobling's experimental studies are of interest at this time Jobling did not claim, nor did he suggest, that he had discovered the cause of pellagra, he merely reported his results, hoping that others might carry on the work to determine whether or not the fungus which he isolated from the feces of 6 out of 25 cases studied could be isolated in a large number of cases of pellagra

The Committee on Nutrition of the American Public Health Association, of which Henry C Sherman, Professor of Food

Chemistry of Columbia University, was chairman, in their report on pellagra in 1926 were so impressed with Jobling's studies that they suggested further investigations along the same line, but no reference of any attempt to corroborate Jobling's findings can be found in the literature on pellagra



Fig 5—Experimental lesions of feet and legs in pellagrin after exposure to sun There was no eruption on feet before exposure to sunlight (Courtesy of Ruffin and Smith Duke University School of Medicine)

Researches of Smith and Ruffin—No more thorough and scientific investigations on pellagra have been made anywhere in the world than those carried out by the Duke University group in their study of 465 cases Smith and Ruffin's investigations on the *effect of sunlight on the clinical manifestations* of pellagra proved definitely that not only exposure to the direct rays of the sun, but heat from an electric heater will produce



Fig. 6.—Unilateral dermatitis of one foot and leg, after exposure to sun. (Courtesy of Ruffin and Smith, Duke University School of Medicine.)

the skin lesions and precipitate oral, gastrointestinal and neurologic symptoms in convalescent pellagrins

Comparatively few cases of endemic pellagra occur in midwinter, but reports show that in May, June, and July there are more cases than during the other nine months of the year No doubt there are many potential pellagrins in midwinter who develop skin lesions, and the "diarrhea, dermatitis, and dementia" when they are exposed to the sun in spring and early summer It is probable that many other persons who are pellagrins are never diagnosed as such, because they are not exposed to sunlight and therefore do not develop the classical symptoms of the disease

No one contends that exposure to the sunlight alone will bring on pellagra, but an individual who is in a state of nicotinic acid deficiency, either primary or secondary, when exposed to sunlight may develop the skin lesions, the alimentary trac[t] symptoms, and the nervous manifestations of pellagra N[or] is it contended that persons do not have the skin lesions a[nd] other manifestations of pellagra without exposure to sunlight Sydenstricker and Spies both report the development of pellagra, or the recrudescence of symptoms in pellagrins, who were in hospital wards and not exposed to the direct rays of the sun

The Sunlight Factor in Secondary Pellagra Associated with Ariboflavinosis —A recent case of acute pellagra complicated by riboflavin deficiency secondary to carcinoma of the colon, in which I was called in consultation will illustrate the relation of sunlight to pellagra

CASE REPORT —A man, aged 60 years, following a resection of the colon for carcinoma, developed disgust for food, nausea, vomiting loose bowels a severe degree of oral sepsis with marginal redness of lips, fissures in the corners of his mouth, and pigmentation of the ala of the nose There were no other skin lesions His tongue was fiery red and very sore He was very much depressed physically and mentally The response to nicotinic acid (100 mg) intravenously three times a day riboflavin and the liver extract intramuscularly was dramatic He also was given a blood transfusion In a few days he was able to get out of bed and was placed in a wheel chair and carried to the roof garden of the hospital His surgeon instructed the nurse to let him lie in the sun for a few minutes The following day he developed the typical acute dermatitis of pellagra on the dorsal surfaces of his hands and on his forehead and cheeks the sore mouth and red tongue reappeared his bowels became loose, and he was de

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coproporphyrin They called attention to the increase of coproporphyrin in lead poisoning, cirrhosis of the liver, arsenical dermatitis, and cinchophen poisoning It is interesting to note that in all the conditions in which an increase in urinary coproporphyrin has been observed liver pathology is the outstanding finding at autopsy May it not be possible that positive tests for porphyrin in the urine in pellagra and the other conditions mentioned are evidences of liver insufficiency and not a specific test for pellagra?

It would seem worth while to determine, if possible, by further experiments, whether or not nicotinic acid, or other liver fraction, has any relation to porphyrin metabolism and the sensitization of pellagrins to sunlight Certainly there seems reason to suspect that liver insufficiency may result in disturbed porphyrin metabolism, thus sensitizing nicotinic acid deficiency victims to sunlight

CHAPTER XII

THE GENESIS OF PELLAGRA — THE AUTHOR'S VIEWS

Deficiency of Nicotinic Acid—the Essential Factor.—A deficiency of nicotinic acid in the human body is now generally considered as the essential factor in the etiology of pellagra. The experimental investigations of Elvehjem in which he cured blacktongue in dogs by the use of nicotinic acid derived from liver extract were the basis for his suggestion that nicotinic acid may cure pellagra in human beings. The contemporaneous clinical studies by Ruffin and Smith, Spies and his associates, Fouts and associates, Sydenstricker and others, in which nicotinic acid was successfully used in the treatment of human pellagra, seem to prove that it is the Goldberger pellagra preventive factor in vitamin B.

It will be remembered that Casimir Funk, who coined the word vitamin to denominate the substance in food which protects against beriberi, suggested in 1911 that pellagra may be due to a deficiency of one of the factors in vitamin B. It also is interesting to note that Casimir Funk found that yeast was rich in vitamin B, and that he isolated from yeast three substances which he believed to be component factors in vitamin B. Funk used nicotinic acid in his experimental studies on beriberi in 1912. He found that nicotinic acid alone would not cure beriberi, but he observed that the victims of this vitamin B deficiency disease improved more rapidly when given that substance which he isolated from yeast.

Goldberger, in 1923, postulated the existence of a pellagra preventive factor in vitamin B, and he and his associates, including Wheeler, Lillie and Sebrell, then began experiments on animals which seemed to show that yeast contains a factor which protects them against blacktongue, considered as analogous to pellagra in human beings. Goldberger also popularized the use of yeast both in the treatment and prevention

coproporphyrin. They called attention to the increase of coproporphyrin in lead poisoning, cirrhosis of the liver, arsenical dermatitis, and cinchophen poisoning. It is interesting to note that in all the conditions in which an increase in urinary coproporphyrin has been observed liver pathology is the outstanding finding at autopsy. May it not be possible that positive tests for porphyrin in the urine in pellagra and the other conditions mentioned are evidences of liver insufficiency and not a specific test for pellagra?

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of human pellagra It now is an accepted conclusion by many that nicotinic acid is the Goldberger preventive (P P) factor in yeast

Granting that a deficiency of nicotinic acid is the essential factor in the production of pellagra, what are the underlying causes of this type of avitaminosis? They seem to be many, including both extrinsic and intrinsic, or exogenous and endogenous, factors

Extrinsic Factors—The extrinsic or exogenous, factors in the genesis of pellagra seem to be as follows

1 A deficiency of nicotinic acid in the diet

2 The ingestion of toxins in beverages and foods over a long period of time, which cause gastrointestinal disease and liver insufficiency or liver pathology, thus preventing the storage and utilization of nicotinic acid

3 The ingestion of food, or water, carrying pathogenic bacteria, or disease producing protozoa or the larvae of ankylostoma and other intestinal parasites which, by causing chronic diseases of the gastro intestinal tract and secondary liver insufficiency, prevent the utilization of nicotinic acid by the human body

Intrinsic Factors—The intrinsic, or endogenous, factors, which are underlying causes of nicotinic acid deficiency appear to be pathologic physiology of the stomach and liver, with and without demonstrable pathologic changes in those organs There seem to be valid reasons for believing that gastric and hepatic insufficiency may be primary and important factors in producing the nicotinic acid deficiency which is essential for the production of pellagra

The Gastric Intrinsic Factors—Sydenstricker postulated gastric deficiency as an intrinsic factor in pellagra, based upon the studies of Castle and the late Roger Morris, in which it was shown that there exists an "intrinsic" gastric factor in pernicious anemia Sydenstricker cured a number of cases of pellagra first by the use of the syphoned contents of the stomach of normal human beings, and later by the use of the gastric secretions and extracts prepared from scrapings of the mucosa of the stomach of animals Spies, and Petrie and his associates repeated Sydenstricker's experiments with the same results There can be little doubt that Sydenstricker's gastric intrinsic factor plays an important part in the genesis of pellagra

The Liver Intrinsic Factor.—The premises for postulating the existence of a liver intrinsic, or endogenous, factor in pellagra are the following

(a) Liver and liver extracts cure pellagra

(b) The liver is a depository of all the vitamins

It is known that nicotinic acid is present in the normal liver It will be recalled that Elvehjem used nicotinic acid derived from liver extract in curing blacktongue in dogs According to Sydenstricker the nicotinic acid content of normal liver may amount to 25 mg per 100 c c of liver McCollum, in the new revised rewritten, fifth edition (1939) of his monumental book *The Newer Knowledge of Nutrition* in which are summarized all of the important advances in vitamin studies concludes that the body, including the liver, has little power to store up vitamin B_1 (thiamin) It, therefore may be assumed that the nicotinic acid and other factors in vitamin B complex must be replenished constantly in order to prevent avitaminosis Sydenstricker postulated that hepatic insufficiency prevents the storage and utilization of nicotinic acid

(c) Pathologic physiology of the liver, with or without hepatic pathology, appears to be an essential factor in the genesis of pellagra The premise for this postulate is that pathologic changes in the liver have been found to be present almost constantly in necropsy studies on pellagrins The late H F Harris, in his book on pellagra, containing the most comprehensive review of the literature on pellagra ever published (1918), pointed out that autopsy studies on pellagrins carried on for more than a century by Italian pellagrologists showed liver pathology as an almost constant finding

Liver Pathology in Pellagra.—Perhaps the most thorough studies on the pathology of pellagra ever made in the United States were carried on from 1910 to 1912 by the Illinois Pellagra Commission, of which the late Frank Billings was chairman The pathologists who performed the autopsies and who made the histologic studies in the Illinois cases were impressed by the constant pathology they found in the liver The Illinois Pellagra Commission expressed the opinion that the liver damage was secondary to gastrointestinal infections and infesta

It may not be possible to demonstrate pathology of the liver and stomach in every case of pellagra any more than it can be proved that there are pathologic changes in the islet cells of the pancreas in every case of diabetes mellitus, yet diabetes mellitus is accepted as essentially a pancreatic disease due to a deficient secretion of insulin Shields Warren, associated with Joslin, found in 259 autopsies on diabetic patients 69 (26 per cent) in which there was no demonstrable pathology of the pancreas In the 190 cases of diabetes in which Shields Warren found changes in the islets of the pancreas, no pathology was found which could be considered distinctive of diabetes In other words the same pathology that is found in the pancreas in diabetes is encountered in other diseases in which there is no disturbance of carbohydrate metabolism

It appears from a study of the literature on pellagra that liver pathology can be demonstrated in as large a proportion of cases as pathologic changes in the pancreas can be shown to exist in diabetes It is entirely possible that a person may have liver insufficiency, and even a subacute or chronic hepatitis in pellagra, and at autopsy no changes in the liver can be demonstrated, just as Shields Warren, an eminent pathologist, could find no pathology of the pancreas to account for diabetes in 26 per cent of post mortems on diabetic patients Likewise pathology of the stomach cannot be proved in every case of pellagra, yet it is known that in the great majority of cases the hydrochloric acid secreting function of the stomach is impaired and sometimes permanently destroyed

The Gastric and Liver Intrinsic Factors in Alcoholic Pellagra —Alcoholic pellagra is assuming serious proportions in the United States, and the use of beverages containing ethyl alcohol to excess over a long period of time is known to be one of the underlying causes, the primary factor, in the production of many cases of pellagra Spies, Blankenhorn, J B McLester and their associates in their extensive and comprehensive studies on pellagra in Cleveland, Cincinnati, and Birmingham seem to have proved that alcoholic pellagra is identical with endemic pellagra and that nicotinic acid deficiency is the essential factor in its production

Since the predisposing cause of alcoholic pellagra is a known toxin with predilection to liver damage, and nicotinic acid deficiency has been proved to be the exciting factor in the disease, the genesis of alcoholic pellagra will be considered first It seems probable that the first step in the genesis of alcoholic pellagra is the irritating effect of strong solutions of the known toxin, ethyl alcohol (40 to 50 per cent in whiskey, brandy, and gin), upon the mucosa of the stomach and upper intestines Secondary infection of the stomach, intestines, and colon follows Thus chronic gastritis with hypochlorhydria, or anachlorhydria, and gastric insufficiency, the loss of the gastric intrinsic factor in pellagra, are sequences of chronic alcoholism

In chronic alcoholic gastritis, with achlorhydria, the fermenting, undigested, alcohol laden contents of the stomach are emptied into the intestines, and soon the mucosa of the intestines loses its power to repel invasion by pathogenic bacteria and chronic enterocolitis results First, there is intestinal stasis with constipation and then diarrhea follows "the drunkard's diarrhea"

The effect of alcohol on the liver is well known The late William H Welch found that liver pathology of varying degrees is a constant pathologic finding in necropsies on chronic alcoholics, Laennec's cirrhosis being the terminal stage of a chronic hepatitis Long before cirrhotic changes of the liver can be demonstrated in alcoholics fatty infiltration and fatty degeneration occur and liver insufficiency must result, and since one of the many functions of a busy liver the central biochemic and *physiologic laboratory of the human body, is to store up* for utilization all the vitamins, enzyme activators, one can visualize nicotinic acid deficiency as a sequence of chronic alcoholism When nicotinic acid deficiency as a result of liver insufficiency becomes pronounced the symptoms of pellagra appear, and, if the victims continue the use of their favorite toxic narcotic, ethyl alcohol, they die of pellagra before the manifestations of cirrhosis of the liver are evident The fact that the symptoms of pellagra in alcoholics will clear up with the use of nicotinic acid, or liver extract containing nicotinic acid, is strong evidence that liver insufficiency is present in alcoholic

pellagra. It, therefore, seems evident that there must be an intrinsic factor in the liver in alcoholic pellagra.

It has been suggested that pellagra in alcoholics is due to an insufficient intake of food containing the pellagra-preventive factor in vitamin B, now believed to be nicotinic acid, and no doubt that may be a factor, but it is not the only factor. Rutledge, Dearman, and Spearman and Smith each reported a case of a patient with alcoholic pellagra in whom the skin and oral lesions disappeared after omitting alcohol, without change of diet. Spies and associates caused the subjective symptoms of pellagra to disappear, even though they continued the use of alcohol, by the use of a full diet, yeast and nicotinic acid. It may be assumed that in alcoholism there is always liver damage, with hepatic insufficiency, and since nicotinic acid storage, or utilization, seems to depend upon a normally functioning liver, it appears that Spies and his associates in using yeast and nicotinic acid in alcoholic pellagra were employing replacement therapy. Reasoning a little further it seems probable that a damaged liver is the underlying factor, though it may not be the only factor, in alcoholic pellagra.

It seems probable that liver damage following the long continued use of alcohol is the most important factor in the production of nicotinic acid deficiency in alcoholic pellagrins.

The Genesis of Pellagra in Which Corn Toxins May Be Factors—Men's opinions may change but facts remain the same always. In 1912 at the National Pellagra Conference in Columbia, South Carolina, there was remarkable unanimity in the expressed opinions of the speakers, who had large experiences in dealing with pellagra, that toxins in spoiled corn are the cause of pellagra. In five years the opinions of many physicians had changed regarding the etiology of pellagra, and it then was the mode to believe that "the unbalanced diet, low in proteins (certain amino acids)" was the cause of pellagra. When that theory was abandoned in 1923, without its proponents ever admitting their error, the pellagra preventive factor in vitamin B, or vitamin B or vitamin G, became the medical fashion, but the facts presented in 1912 are facts in 1940.

The evidence showing that corn toxins are predisposing factors in the production of pellagra cannot be ignored, but I do

not believe that these are the only factors or even the most important underlying factor in nicotinic acid deficiency It seems probable that in some cases toxins in corn bread mush (polenta), grits, hominy, and other products may bear the same relation to endemic pellagra that the toxin, ethyl alcohol, in whiskey and other alcoholic beverages, has to alcoholic pellagra

The chemical formula of ethyl alcohol is C_2H_5OH, while Lombroso's "pellagrazein" found in fermenting corn, and other cereal grains, belongs to the group of phenols the best known of which is ordinary phenol phenylic alcohol, C_6H_5OH Chemically the only difference between ethyl alcohol and the phenols, of which pellagrazein is one, is the rearrangement of the hydrocarbon molecules If ethyl alcohol can cause the avitaminosis which results in pellagra in those who use that toxin, may not the use of musty meal made from spoiled corn, containing a phenol derived from fermenting grain, bring about the same condition?

Granting that there are toxins in the corn meal products so largely consumed in the sections of the United States in which pellagra is endemic it would seem that their action on the stomach, intestines, and liver would be much the same as that described in discussing the genesis of alcoholic pellagra In other words, it would seem that the pathology produced by "pellagrazein" and other corn toxins in the liver would prevent the storage or the utilization of nicotinic acid, the pellagra preventive factor Thus nicotinic acid deficiency in pellagra resulting from the ingestion of toxins in corn products appears to be one of the many predisposing causes of the disease Numerous reports show that when corn products are left out of the diets of pellagrins in regions in which they are the principal source of food the victims have been restored to health

Endogenous Toxins and Pellagra—In the late eighties the ravages of pellagra in southern Austria and in Rumania assumed such serious proportions that Neusser the great Viennese Clinician, Professor of Medicine in the University of Vienna was sent by the Austrian government to investigate the causes of the disease, and to recommend measures for its prevention Neusser and his associates made careful studies of the possible etiologic factors He came to the conclusion that the relation

of maize to pellagra occurs when the digestion is impaired and a toxin forms from the fermentation of corn products in the intestines, this toxin will produce all the symptoms of the syndrome known as pellagra Neusser's report of 131 pages published in 1887 was an important contribution to the accumulated knowledge of pellagra

While Neusser was convinced that the use of fermenting maize was the primary cause of pellagra, he believed that the toxin causing pellagra was an endogenous product formed in the intestines by the action of the *Bacillus maidis* He was of the opinion that the individual with normal digestive apparatus was not affected by the toxins formed in what he called the "mother substance" (*"substantia mater"*) but if there was impaired digestive secretion, as in achlorhydria, the toxins formed by the *Bacillus maidis* acting on the "mother substance" in the intestines became deleterious to health and finally resulted in pellagra

It is interesting to note that Neusser considered that the toxin generated by the *Bacillus maidis* in the intestines was similar to ethyl alcohol Neusser observed that all the alcohol used by the Rumanians was made from corn, and he believed that the use of alcohol made from deteriorated maize is one of the causes of pellagra He considered the use of alcoholic beverages as a predisposing cause of pellagra, because they produced "gastro enteric catarrh and depressed the organism" Neusser in his chemical studies found an aldehyde, related to alcohol, which he thought was produced by the decomposition of resins and glucosides resulting from the fermentation of deteriorated maize in the intestines

Neusser's studies cannot be disregarded in considering the genesis of pellagra He did not prove that toxins generated in the intestines from fermenting maize are the sole cause of pellagra, but considering the fact that toxins formed in the intestines are carried in the blood stream directly to the liver, and that liver damage and liver insufficiency would result, his studies certainly suggest that the ingestion of corn meal, contaminated by the *Bacillus maidis* and other maize fungi, is a predisposing cause of pellagra If such is a fact toxins formed in the intestinal tract from fermenting maize products, "sour

mash" as Yarbrough called it, bear the same relation to pellagra that ethyl alcohol does to alcoholic pellagra, in that by their action on the liver they are a cause of nicotinic acid deficiency

Deeks' High Carbohydrate Diet Theory—Deeks' theory of the genesis of pellagra deserves more than passing consideration He believed with Neusser, though his conclusions were arrived at independently, that toxins formed in, and absorbed from, the intestinal tract affect nutrition, resulted in pellagra and many other diseases Deeks postulated, though he admitted that it has not been proved, that in the evolution of man he has become biologically unable to digest and metabolize an excess of purified cane sugar products and other devitaminized carbohydrates as white flour white meal and white rice He believed that when an excess of carbohydrates was ingested daily over a period of years the first effect is gastric and intestinal digestion, and that as a result fermentation of food begins in the stomach and increases in the intestines As a result of the bacterial activity in the intestines, toxins, such as the aldehydes and the kindred groups of alcohols, were formed, and as a sequence, there is infection of the gastrointestinal tract, i e, gastroenterocolitis

Deeks also believed that hepatitis follows the gastroenteritis and that the resulting damage to the liver affects general nutrition He also believed, what was later proved by McCarrison, that ulcers of the stomach, gall bladder infection, and colitis and other abdominal infections may be caused by high carbohydrate, vitamin deficient diets

The Role of Infections in the Genesis of Pellagra—Deductions drawn from a study of the literature on pellagra convince me that pellagra is not due to any specific infection It seems probable, however, that many infections and infestations of the human body, particularly of the gastrointestinal tract by producing liver insufficiency may be predisposing causes of importance in producing nicotinic acid deficiency, the essential factor in the genesis of the disease

The infections theory of pellagra was believed in by many capable Southern physicians for the reason that the disease is most prevalent in spring and summer in the rural districts where

soil pollution is practiced Pellagra has been found so frequently in victims of malaria, amebiasis, and uncinariasis, who reside in rural districts and in the unsewered and poorly drained sections of cities, that no one who considers the relation of cause and effect can doubt that these diseases are predisposing factors in the production of pellagra

It also is a fact, that with the development of efficient health departments in the states in which pellagra is most prevalent, carefully conducted campaigns against rural diseases, particularly those due to soil pollution, have resulted in a marked reduction in the morbidity and the mortality from malaria, amebic dysentery, and hookworm, diseases which have a predilection for producing liver insufficiency or actual liver pathology Note the more or less constant liver pathology found in fatal cases of malaria and in intestinal infestations, such as abscess of the liver in amebiasis Also that severe anemia, probably of liver origin, may be an outstanding feature of malaria, chronic gastrointestinal infections, amebiasis, uncinariasis, and pellagra The infections theory of pellagra may be correlated with the nicotinic acid deficiency conception of the disease, by considering malaria, amebiasis, uncinariasis, and other tropical diseases as causes of hepatic insufficiency, causing inability of the liver to store up or utilize nicotinic acid

Kenneth Lynch, Professor of Pathology in the University of South Carolina, in 1916, reported pathologic studies showing almost constant lesions of the intestines, particularly in the sigmoid and rectum, in pellagra Lynch found *Endamoeba histolytica* in such a large proportion of cases that he said in substance "When we find the reasons for the decrease in amebiasis in the South we shall find the cause for the decrease in pellagra" In the light of our present knowledge of pellagra, it seems probable that amebic dysentery, with its predilection for producing liver damage, first insufficiency and then abscess of the liver, is one of the causes of nicotinic acid deficiency, the *sine qua non* in the genesis of pellagra In other words pellagra is in many cases secondary to amebic dysentery and other diseases of the gastrointestinal tract John Jelks, a Proctologist of Memphis, Tennessee, found *Endamoeba histolytica* so fre

quently present in rectal examination of pellagrins that he has maintained for twenty five years that pellagra is secondary to amebiasis

Liver Damage Secondary to Gastrointestinal Diseases—When it is remembered that the blood supply of the gastro intestinal tract, including the rectum, drains directly into the hepatic vessels, it is not difficult to believe that the toxins formed in the intestines as a result of bacterial invasion, or from protozoan intestinal infestations, so damage the liver cells that they cannot store up or utilize nicotinic acid

Actual infections of the liver, acute and chronic hepatitis, usually are secondary to intestinal diseases Cholecystitis and hepatitis may follow a duodenitis, extending, by continuity from the duodenum through the common duct into the hepatic ducts and into the liver cells, or the micro organisms of various infections, or the pathogenic protozoa (*Endamoeba histolytica*), may be carried to the liver in the blood stream from lesions in the small intestines, colon, and rectum Certainly liver insufficiency may result from chronic gastrointestinal infections and infestations, depending upon the amount of liver tissue involved and the severity of the infection

Secondary Pellagra—Pellagra has been noted frequently as a sequel, and sometimes as a terminal condition, of organic diseases of the gastrointestinal tract particularly in carcinoma of the esophagus, stomach, intestines, and rectum It also has been observed in gastric and duodenal ulcers, chronic gastritis, chronic enteritis, and ulcerative colitis in a number of cases Any patient with ulcerative colitis should be regarded as a potential pellagrin Pellagra has been found as a complication of rectal diseases perhaps more frequently than in any other portion of the alimentary canal

Probably the most thorough study of secondary pellagra as related to associated diseases of the gastrointestinal tract was made in Charity Hospital in New Orleans, in 1929 by Roy H Turner, Assistant Professor of Experimental Medicine in Tulane University Turner made autopsies in 16 fatal cases of pellagra which developed following primary alimentary tract lesions Of Turner's patients 8 had stricture of the rectum, 2 had colitis, 1 probably tuberculosis and 1 each of the following conditions

gumma of the stomach, rectovaginal fistula and syphilitic proctitis, partial stenosis of the jejunum due to old tuberculous ulcer, partial stenosis at the ileocecal valve due to bands of adhesions, and amebic dysentery

Turner's 16 fatal cases of secondary pellagra were among 75 cases of pellagra seen by him during a given time Turner is of the opinion that pellagra, as a sequel, or as a complication, of serious organic diseases of the gastrointestinal tract, occurs more frequently than is generally realized

Turner found so large a proportion of his cases with absence of free hydrochloric acid that he concluded "Until the etiology of the disease is better understood I believe one is justified in suspecting that this deficient secretion may play an important part in the production of pellagra in many cases"

W M Scott, in 1937, reported 15 cases of "secondary pellagra" among 87 admissions of pellagrins in the Shreveport Charity Hospital Seven were associated with typical lesions in the rectum in victims of lymphogranuloma inguinale, 2 with carcinoma of the stomach, 2 in malignancy with metastasis and 1 each of the following stricture of the esophagus, rectal polyp, rectovaginal fistula, and amebiasis

It should be remembered that Turner and Scott were dealing with charity patients, among neglected, poorly nourished individuals who if they had not died of pellagra would have died of the primary diseases It is to be expected that the incidence of secondary pellagra would be much higher among indigent patients who go to hospitals as a last resort

Eusterman and O'Leary reported 13 cases of secondary pellagra at the Mayo Clinic in 1931 The primary lesions in the 13 cases were as follows 2 cases of pyloric obstruction due to duodenal ulcer, 1 pyloric obstruction (carcinoma), 2 duodenal ulcer and malfunctioning gastroenterostomy, 1 pyloric obstruction with gastric ulcers and chronic cholecystitis, 1 gastric ulcer (jejunal feeding), 1 gastric syphilis, 1 esophageal stricture, 2 unnecessary gastroenterostomies, 1 carcinoma of the colon, and 1 ulcerative colitis

I have seen a number of cases of secondary pellagra, in 3 recent cases, 1 complicating carcinoma of the esophagus and 2

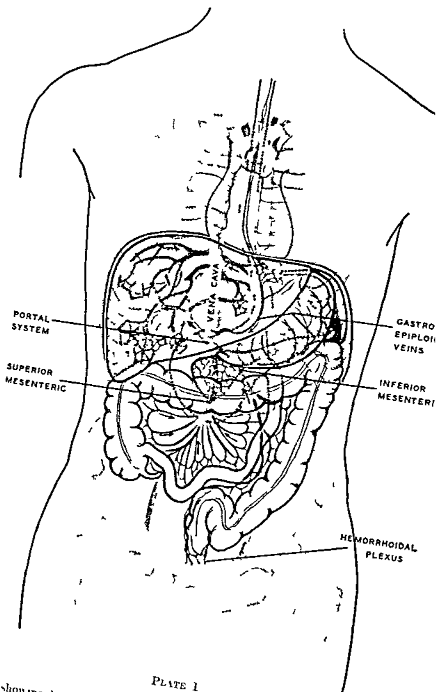


PLATE I

Diagram showing how the veins of the stomach, intestine, colon and rectum may carry toxins and infections to the liver through the portal system. Liver damage causing liver insufficiency prevents the storage and utilization of nicotinic acid, the pellagra preventive factor in vitamin B.

following operations for malignancy of the sigmoid It will be remembered that secondary infection with pathogenic bacteria occurs frequently in carcinoma of the alimentary tract, and it may be assumed that toxins generated by the neoplasm and by secondary infections in the gastrointestinal tract will be carried to the liver Thus liver damage and hepatic insufficiency develop with nicotinic acid deficiency and pellagra as the sequence

It would appear that liver damage secondary to many diseases, particularly of the gastrointestinal tract is responsible for the deficiency of nicotinic acid and the multiple avitaminoses in pellagra, more than an inadequate intake of food in such cases

High Carbohydrate Diets—Goldberger may have erred in asserting that an unbalanced diet low in proteins is the one and only cause of pellagra, but there can be no question that an insufficient intake of proteins and a preponderance of carbohydrate consumption over a long period of time lower resistance, and are predisposing causes of pellagra

Studies of the carbohydrate protein and fat content, and the vitamin constituents of the diets in the districts in which pellagra prevails reveal the fact that they are deficient both in proteins and in all the vitamins, particularly the B complex Certainly a diet made up largely of Western ground corn meal bread, syrup, and side meat (bacon) such as many of the inhabitants of pellagrous districts consume is the most important factor in the production of pellagra in the South That such a diet predisposes to gastrointestinal infections there can be no doubt, and gastroenteritis is followed by insufficiency of the stomach and liver Thus the gastric and liver intrinsic factors which protect against pellagra are impaired or destroyed and pellagra develops

That a high carbohydrate diet interferes with the catalytic effect of thiamin in tissue respiration is now believed, and it may be assumed that nicotinic acid is an enzyme activator with similar function in the metabolism of carbohydrates It is an interesting fact that Casimir Funk who in 1912 predicated that pellagra is due to a deficiency of a factor in vitamin B and who

isolated nicotinic acid from yeast observed, in 1914 (cited by McCollum), "that an increase in carbohydrate ingestion causes a more rapid production of polyneuritis in pigeons on a thiamin deficient ration"

McCollum also cites the more recent studies of Kauffman Cosla and their associates as showing that "thiamin deficiency is accompanied by a progressive diminution in carbohydrate tolerance"

There is no proof that a high carbohydrate diet interferes with the catalytic action of nicotinic acid as it does in "the oxidative removal of the lower degradation products of glucose metabolism" as Peters and his co workers have shown occurs with thiamin, but it may be assumed that such is a fact Deeks, in 1910, in studying the diet of pellagrins under his care in the Ancon Hospital in the Panama Canal Zone, became convinced that a high carbohydrate diet is the cause of pellagra, and he found that a diet low in carbohydrates and high in proteins cured the disease Deeks later pointed out that diets high in carbohydrates, particularly the cane sugar products, also are deficient in all the vitamins, including the pellagra preventive factor More recent studies by Spies and others seem to show that the action of nicotinic acid is interfered with when an individual's diet is inordinately high in carbohydrates

Williams and Spies, in their excellent monograph *Vitamin B_1 and Its Use in Medicine,* point out that the thiamin requirement is greatly increased when there is an excess of carbohydrates in the diet, and that in such cases thiamin deficiency develops rapidly It may be assumed that the nicotinic acid requirement of the body is increased when high carbohydrate diets are used and that nicotinic acid deficiency to the degree of producing pellagra will follow the long continued use of food in which there is a marked excess of corn bread and syrup as principal articles of food

While it has not been proved there is reason to assume, as a working hypothesis, that in the prevention and treatment of pellagra, a high carbohydrate, low protein diet predisposes to pellagra, and that a high protein and a low carbohydrate diet, in addition to adequate vitamin content, is essential in the treatment of the disease

Conclusions

The following factors in the genesis of pellagra have been discussed

1 The genesis of pellagra in which the primary factors, or predisposing causes, are ethyl alcohol, toxins in spoiled corn, gastrointestinal infections or infestations, carcinoma, and other chronic diseases of the alimentary canal

2 The role of avitaminosis in producing gastrointestinal infections and liver pathology

3 Relationship to pellagra of the multiple vitamin deficiencies resulting from the long continued use of diets insufficient in proteins and high in carbohydrates

4 Many factors, both extrinsic and intrinsic, may be operative in the genesis of pellagra, though nicotinic acid deficiency is the exciting cause

Extrinsic Factors in the Genesis of Pellagra 1 Primary nicotinic acid deficiency due to inadequate intake of the pellagra preventive factor in food

2 The ingestion of toxins in alcoholic beverages or of "pellagrazein in foods containing fermenting corn products, producing pathology or pathologic physiology of the gastrointestinal tract, and liver with secondary nicotinic acid deficiency

Gastric and Hepatic Intrinsic Factors in the Genesis of Pellagra 1 Pathology or pathologic physiology of the stomach resulting in a deficiency of the gastric intrinsic factor in pellagra

2 Pathology or pathologic physiology of the liver producing secondary nicotinic acid deficiency, because of the inability of the liver to store up or to utilize nicotinic acid

The Role of Sunlight in the Genesis of Pellagra Exposure to sunlight produces skin lesions in patients with subclinical pellagra in such a large proportion of cases, there can be no doubt but that sensitization to the sun's rays is a precipitating cause of an exacerbation of symptoms Skin lesions and other manifestations of pellagra may occur, however, without exposure to the sun

Suggested Experimental Studies Recent experimental and clinical studies on the relation of avitaminosis to pellagra have been productive of important advances in the knowledge of the

etiology and treatment of the disease, but laboratory and clinical investigations on the primary or predisposing causes of nicotinic acid deficiency should be continued

The following suggestions for such studies are submitted

1 The relation of avitaminosis to gastrointestinal infections and to liver pathology

2 Continued pathologic studies of the stomach and liver in human pellagra

3 Studies in pathologic physiology of the stomach and liver in blacktongue in dogs

4 Bacteriologic studies of corn fungi, and investigations to determine whether or not toxins formed by them will produce nicotinic acid deficiency in animals and in undernourished human beings

5 The relation of the liver to the metabolism of coproporphyrin and allied substances in producing sensitization to sunlight in cases of nicotinic acid deficiency

CHAPTER XIII

PELLAGRA, PERNICIOUS ANEMIA, AND SPRUE

I do not believe that pernicious anemia, pellagra, and sprue are different manifestations of the same disease, but, on the contrary, it is evident that they are three separate and distinct disease entities. There are, however, symptoms which may be common to the three diseases, including all the gastrointestinal symptoms, nervous manifestations, and macrocytic anemia. For instance, given an adult patient with achlorhydria, stomatitis, diarrhea, mental depression, and the motor manifestations resulting from involvement of lateral and posterior columns of the spinal cord and severe anemia, without skin lesions, it may be impossible to make a positive diagnosis of pellagra, pernicious anemia, or sprue. The addition of a symmetrical, bilateral, pigmented, exfoliative, erythematous dermatitis of the dorsal surfaces of the hands and feet to symptoms which may be common to sprue and pernicious anemia enables the clinician to make a diagnosis of pellagra, while the large, fatty, fermenting, pasty clay colored stools in a patient with stomatitis, diarrhea, and severe anemia, may be the only pathognomonic difference between sprue and pernicious anemia. The patient with stomatitis, diarrhea, mental, sensory and motor symptoms and anemia without skin lesions who resides in a community in which pellagra exists would be regarded as a probable pellagrin. Likewise the patient with the same symptoms, who resides for instance in Porto Rica in which sprue is endemic, with only an occasional case of pellagra, would be diagnosed as having sprue.

Gastrointestinal Symptoms in Pernicious Anemia.—Richard Cabot said that diarrhea was present in the majority of his cases of pernicious anemia, and the Boston patient with macrocytic anemia, stomatitis, diarrhea, and the nervous manifestations common to these three chronic diseases would be diagnosed as a victim of typical Addisonian anemia.

William Murphy's description of the gastrointestinal tract symptoms of pernicious anemia in his new book (1939) on

Anemia (p 89) might apply as well to the subclinical type of pellagra before skin lesions appear as when there are no skin lesions present He mentions as symptoms of pernicious anemia "sore tongue or sore mouth, diarrhea, anorexia, nausea and vomiting, and achlorhydria " All of these symptoms also occur in pellagra Mental symptoms are frequent in pellagra, and less frequent in pernicious anemia Murphy, in discussing psychoses in pernicious anemia, said that psychotic symptoms may occur when the red blood counts are low



Fig 7 —Photomicrograph of section of liver in a fatal case of pellagra showing atrophy and cellular infiltration (Courtesy of J W Goodpasture, Professor of Pathology Vanderbilt University)

When the diagnosis of pernicious anemia, pellagra, or sprue is made the treatment found most effective in all of them is liver, or liver extract and a high protein, relatively low carbohydrate rich vitamin diet—practically the only difference being that in pernicious anemia liver or liver extract must be continued for the rest of the patient's life

Similar Pathology in Pellagra, Pernicious Anemia, and Sprue—In the great majority of cases there is pronounced liver pathology fatty degeneration usually in pellagra, pernicious anemia, and sprue In the chapter on pathology a number of

writers have been cited who called attention to the changes in the liver in pellagra It is enough to cite Sir William Osler as saying that in pernicious anemia 'the liver may be enlarged and fatty In most of my autopsies it was normal in size, but usually fatty '' Atrophy of the stomach may be seen in all three diseases, and the permanent subacidity and anachlorhydria are evidences of damage to the hydrochloric acid forming cells in the stomach in pellagra sprue, and pernicious anemia Atrophy of the intestines may be seen in all three diseases Likewise

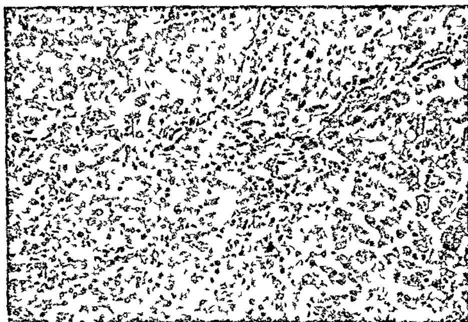


Fig 8—Photomicrograph of section of liver in case of pernicious anemia, showing atrophy and pigmentation (Courtesy of J W Goodpasture Professor of Pathology Vanderbilt University)

there is marked similarity in the pathology of the lateral and posterior columns when there are cord changes in pernicious anemia pellagra, or sprue

The food factor a deficiency diet certainly is much the same in the etiology of pellagra and sprue, and to a less extent in pernicious anemia The etiology of pernicious anemia is admittedly unknown Ashford's theory of the *Monilia psilosis* is not generally accepted as being the cause of sprue and while many believe that a deficiency of nicotinic acid is the cause of the symptoms of pellagra all of the essential factors in the pro



Fig 9 —Photomicrograph of section of spinal cord showing degenerative changes in case of pellagra (Courtesy of J W Goodpasture Professor of Pathology, Vanderbilt University)



Fig 10 —Photomicrograph of section of lumbar cord in pernicious anemia showing degenerative changes (Courtesy of J W Goodpasture, Professor of Pathology Vanderbilt University)

duction of pellagra have not been discovered It certainly seems that it would be advisable to continue investigations into the causes of pernicious anemia, pellagra, and sprue until all the etiologic factors in each have been recognized

Intrinsic Liver Factors in Pernicious Anemia and Pellagra—At the meeting of the Mississippi State Medical Association in May, 1927 (New Orleans M & S J, Sept, 1927) I submitted data predicating the hypothesis that pernicious anemia is essentially a disease of the liver and that pathology of the stomach, resulting in achlorhydria, is an etiologic factor of, or a concomitant condition associated with, macrocytic anemia I then suggested the possibility that the liver, in addition to its many other functions may be an endocrine organ, secreting hormones which control erythrocytolysis and, or, hematopoiesis

Accumulated data showing almost constant pathology of the liver in pellagra and pernicious anemia and the use of liver and liver extracts in the treatment of both diseases seem to be sufficient basis for considering the possibility that the liver and the stomach may secrete synergistic hormones, a deficiency of either one of which results in pernicious anemia, and that liver damage prevents the utilization or storage of nicotinic acid, the cause of pellagra I desire it distinctly understood that I do not assert that the liver and the stomach secrete hormones, deficiency of which is essential for the production of pernicious anemia and pellagra I merely advance the hypothesis of hepatic and gastric intrinsic factors in both diseases, with the hope that experimental and clinical investigations may be undertaken to prove or disprove that the liver and stomach secrete pernicious anemia preventive factors

Pathology of the liver and pancreas are almost constantly associated in sprue Tom Brown of Johns Hopkins, years ago advanced the theory that sprue results from a deficiency of the external secretions of the pancreas and he found that the use of pancreatic extracts controlled the azotorrhea and steatorrhea in sprue—replacement therapy It also has been known for years that the duodenum secretes an endocrine (secretin) which stimulates the external secretions of the pancreas Is it not possible that sprue is essentially a disease of the duodenum

and pancreas, and that when macrocytic anemia is associated with sprue it is due to associated liver dysfunction?

Assuming that chronic hepatitis may bear a relationship to pernicious anemia, pellagra and sprue, what are the etiologic factors of the liver pathology? It would seem that gastro intestinal infections of any kind may damage the liver, either by the absorption of exogenous, or endogenous toxins, or by metastatic infection carried directly from the blood of the stomach and intestines to the liver Infection of the liver may result from the extension of a duodenitis through the common duct to the liver This is shown by the frequent association of chronic cholecystitis and chronic hepatitis In the case of sprue a pancreatitis, by destroying or inhibiting the function of the cells concerned with the external secretions of the pancreas, could result from the extension through the pancreatic duct to the pancreas of the infection responsible for duodenitis

In other words, it would seem that in pernicious anemia, pellagra, and sprue, there is no specific organism responsible for any one of the three diseases, but it appears possible that any or all of the pathogenic organisms that may infect, or infest, the intestinal tract may cause liver pathology This hypothesis fits in with the undoubted vitamin deficiency factor in pellagra for the reason that McCarrison has proved that intestinal in fections follow the use of diets in which there is the lack of essential protective substances in food It also explains how toxins such as ethyl alcohol and "pellagrazein," a phenylic alcohol, derived from spoiled corn, may cause pellagra

There is evidence to show that the liver is involved in porphyrin metabolism and that hepatic damage may be followed by porphyrinemia and porphyrinuria In the opinion of some, the skin lesions of pellagra may be explained by the photo dynamic effect of porphyrinemia, resulting from the effects of endogenous or exogenous toxins in the liver, operative in pel lagra but not in sprue or pernicious anemia Proof of the presence of porphyrinemia in pellagra seems established, but the absence of porphyrin in the urine in sprue and pernicious anemia patients has not been proved

Is Liver Insufficiency the Essential Etiologic Factor in Per nicious Anemia?—In 1927 I submitted data on the etiology of

pellagra and pernicious anemia and outlined my views on the possible relationship of liver pathology to the development of pellagra and pernicious anemia. It was suggested that the liver may secrete endocrines the functions of which are to control erythrocytolysis by stimulation or repression of the reticulo-endothelial system. A hemolytic hormone, a hemolysin, may stimulate the reticuloendothelial system to destroy red blood cells, and an antihemolytic hormone, an antihemolysin, may repress the activity of the blood destroying apparatus. When the hemolytic and antihemolytic hormones are balanced the normal level of 4,500,000 to 5,000,000 red blood cells per millimeter of blood is maintained. If there is a deficiency of the antihemolytic hormone, there is unrestrained hemolysis and pernicious anemia results, and if there is a deficiency of the hemolytic endocrine, polycythemia follows. This hypothesis of the genesis of pernicious anemia fits in with the theory of William Hunter, who in 1888 suggested that excessive red blood destruction rather than inadequacy of the blood forming cells in the bone marrow, is the cause of pernicious anemia.

Liver Hormones?—I have wondered for many years if the liver does not secrete a hormone which working synergistically with the secretion of adrenin by the suprarenals, controls glycogenolysis. The pituitary secretes a number of hormones, which are synergistic with the internal secretions of the thyroid and suprarenal glands and are antagonistic to insulin. Perhaps the liver may secrete many hormones some of which have interrelations with the internal secretions of other organs involved in carbohydrate metabolism. Eosinophilic adenomas of the pituitary are so frequently found with polycythemia that it appears possible that this overworked "master" gland may secrete a hormone which has some relation to hematopoiesis or erythrocytolysis, and that there may be interrelations between the hormones of the pituitary and the liver which affect the number of erythrocytes in the blood. If an eosinophilic adenoma of the pituitary should secrete an excess of a hormone which acts synergistically with a hormone in the liver that represses reticulocytolysis, polycythemia would follow.

The type of clinician who demands pathologic proof before even considering any hypothesis will say that I am wandering

in the realm of speculation when I suggest that the liver may secrete endocrines involved in maintaining stasis of the number of red blood cells circulating in the blood There was a time when the idea that homeostasis of blood sugar was due to the balanced action of antagonistic hormones secreted by the islet cells of the pancreas and the medulla of the suprarenal glands was considered pure speculation, but Cannon and others have proved not only the existence of the hormones of the suprarenals and the pancreas but their antagonistic action to each other Casimir Funk was speculating in 1911 when he suggested that deficiency of a factor in vitamin B is the cause of pellagra, but his hypothesis has been proved Cushing and others did a lot of speculating before they proved that the pituitary is the dominant endocrine organ of the body I offer no apology for suggesting that the liver may secrete hormones, though I admit that I cannot offer proof that such is the case I hope, however, that research workers who are prepared to make biologic laboratory investigations may prove, or disprove, (1) that liver insufficiency is the underlying factor in pernicious anemia, and (2) that hormones secreted by the liver may be factors in erythrocytolysis or hematopoiesis

Identical pathologic changes in the liver are found in pernicious anemia and pellagra It seems possible that liver insufficiency by inhibiting the secretion of an endocrine which controls erythrocytolysis or hematopoiesis may cause pernicious anemia, and that a deficiency of an intrinsic liver factor may prevent the utilization or the storage of nicotinic acid, the pellagra preventive factor in vitamin B

Gastric and Liver Pernicious Anemia Preventive Factors — Greenspon considers it possible that the liver secretes a hormone (endocrine) of which a gastric hormone is the precursor Roger Morris and his associates defined the antianemia principle in the stomach as a hormone because they found that it is "dialyzable, exhaustible and that it withstands chemical treatment known to destroy enzymes " They looked on this substance as "an internal secretion produced by the gastric mucosa "

McCollum cites Ungley, Castle and Hamm, Helmer and Fouts as having controverted Greenspon's theory and his findings, but they have not disproved Greenspon's "working hypothesis" of

the etiology of pernicious anemia being a deficiency of hormones secreted by the stomach and liver

Studies by Castle and Strauss Roger Morris, Greenspon and others on what Castle called the "intrinsic factor," denominated by Roger Morris as an "internal secretion" of the stomach, and by Greenspon as a gastric "hormone," seem to prove a definite relation of impaired gastric function to pernicious anemia

The Interrelations of Vitamins and Hormones—The interrelations of vitamins and endocrines is an intriguing subject which offers a fertile field for speculation, though there is evidence to show that vitamin deficiencies may cause dysfunction or pathology of the pituitary, thyroid and adrenal glands McCarrison, two decades ago, called attention to the relationship of vitamin deficiency to endocrine disorders in relation to diseases of the intestines McCarrison did not discuss pellagra and pernicious anemia as related to intestinal disease but it seems justifiable to assume that the vitamin deficiency which causes hepatic insufficiency and adrenal dysfunction in intestinal infections may under proper conditions produce pellagra or pernicious anemia of which diarrhea is a frequent symptom Naturally the question arises Does liver insufficiency in pellagra and pernicious anemia result in one case in the hyposecretion of an endocrine, and in another prevent the utilization or storage of nicotinic acid in pellagra and a preventive vitamin factor in pernicious anemia? In other words, has it been definitely proved that nicotinic acid is a vitamin and not a hormone, and likewise is there evidence to show that the antipernicious anemia factor is a vitamin and not an endocrine?

McLester on the Nature of Vitamins and Hormones—J S McLester in the recently revised edition of his book *Nutrition and Diet in Health and Disease* expresses what is in the minds of many students of nutrition when he points out the difficulties of determining whether substances necessary for regulating nutrition are vitamins or hormones In discussing the vitamins he says

"They are included under the single generic term vitamin in part for the sake of convenience and in part because they are distinct from other food factors in the minuteness of the amounts required but chiefly because they have in common a regulatory influence upon nu

tritive processes. Reasoning on this basis, however, one can find little justification for distinguishing between vitamins and hormones. In truth, the two have much in common, and it appears that there is good reason for grouping them together. The chief distinction (which does not hold in all instances) is that while hormones are formed within the body by the endocrine organs, vitamins are derived from the outside world through the medium of the food."

Common Etiologic Factors in Pernicious Anemia, Pellagra, and Sprue?—My attention was focused on the possibility of a common etiologic factor in pernicious anemia, pellagra, and sprue by an article on that subject in 1925 by E. J. Wood, Jr., of Wilmington, North Carolina. At that time I was studying a case in which I had observed the transition from typical pellagra into the sprue syndrome and finally into typical pernicious anemia. This patient, who was known to have had achlorhydria when he had typical pellagra in 1916, several years after the dermatitis had cleared up on leaving off the dilute hydrochloric acid developed stomatitis and diarrhea consisting of several large mushy stools a day, and later had severe macrocytic anemia.

My Case of Pellagra, Sprue, and Pernicious Anemia.—A case showing that pellagra, sprue, and pernicious anemia may occur in the same person came under my observation and was reported in 1926.

Case Report.—In 1916 a pronounced pellagrin, male, was found to have stomatitis, achlorhydria, diarrhea, dermatitis, and mild mental depression, with red blood count of 3,800,000. He made a complete recovery following the use of 6 c.c. (1½ drams) of dilute hydrochloric acid in a pint (500 c.c.) of milk with meals and three hours after meals combined with a high protein, rich vitamin diet. He has had no skin lesions of pellagra since 1916. He had sore mouth and a mushy diarrhea when he discontinued the diet and the dilute hydrochloric acid. Thus his symptoms at one time resembled sprue more than pellagra. In 1921, he returned to the clinic with no symptoms of pellagra but presented a typical picture of pernicious anemia, i.e., lemon yellow skin, weakness, achylia, and a red blood count of 1,200,000, later count was 900,000. He was transfused 21 times from 1921 to 1926, usually with temporary benefit; he was kept on a diet consisting largely of milk, meats, vegetables and fruits, a high protein, rich vitamin diet. He gradually grew worse until it seemed the end was near when in 1926 Minot and Murphy's work came out, liver was added to his diet. He liked liver and ate large quantities of it and his red blood count rose in two months to 5,500,000, and he remained in excellent health until in 1936 when he was killed in a cyclone. He not only had the typical blood picture of

pernicious anemia, but was cured by the liver diet Several times both before and after he developed pernicious anemia he tried leaving off the dilute hydrochloric acid with the results that he would have the sprue syndrome i e sore mouth and diarrhea consisting of several large, light colored mushy stools a day

In this case it appears that food deficiency, either in protein or vitamin content, could not have been the only factor in the etiology of the pellagra, sprue, or pernicious anemia The patient was a successful farmer and merchant, who sold his plantation for $35 000 He lived comfortably, and had an adequate diet His wife and college bred children were well nourished, and there were no other cases of pellagra in the family He was living on a liberal well balanced rich vitamin diet when he developed typical pernicious anemia in 1921 He continued this diet without improvement in his symptoms until in 1926 when the addition of liver to his diet brought his blood count from 900,000 to 5,500,000 in two months It is evident that neither food nor vitamin deficiency could have been a factor in producing pernicious anemia in this case The fact that even one individual had pellagra sprue and pernicious anemia in the order named, suggests the possibility of a common etiologic factor in the three diseases

Mallow's Cases of Pellagra and Pernicious Anemia—Other clinicians have observed similarity in some of the manifestations of pellagra and pernicious anemia, and a few cases have been reported in which pellagrins developed typical Addisonian anemia

Mallow pointed out in two articles that in pellagra symptoms of pernicious anemia may manifest themselves He suggested that a study of such cases not only enlarges our clinical knowledge of pellagra but also contributes to the clearing up of the cause of pernicious anemia which unfortunately is not yet known Mallow reported two cases of macrocytic anemia in pellagrins one with a red cell count of 730 000 and another with a count of 700,000 Liver therapy cured both cases

Alessandrini's Case With Symptoms of Pellagra, Pernicious Anemia, and Sprue—Alessandrini a celebrated Italian clinician, in 1934 reported the case of a woman aged 40, who had symptoms of pellagra pernicious anemia, and sprue She had the characteristic pellagra syndrome, including red fissured

tongue, mental depression, and the skin lesions on the backs of her hands. She had 3 or 4 foamy, yellowish stools daily, microscopic examination of which showed large amounts of fatty acids and soap, and many muscle fibers. Examination of the blood showed macrocytic anemia, hemoglobin, 80 per cent, red blood cells, 3,200,000, leucocytes, 3,400, a few normoblasts, macrocytosis, and polychromatophilia. The woman died in an insane hospital four months later. No autopsy was made.

Haden's Cases of Pellagra and Pernicious Anemia.—An important recent contribution to the literature on nutritional disorders is that by Russell L. Haden, of Cleveland, Ohio, in an article entitled "Multiple Specific Nutritional Deficiency Disease in the Adult." Haden discussed particularly that the "present state of our knowledge of the more important specific substances the lack of which leads to nutritional defects in the adult are (1) calcium, (2) iron, (3) vitamins A, B, B (G) and C, and (4) the antipernicious anemia factor." He reported cases of "pernicious anemia and sprue, with low blood proteins", "pellagra and pernicious anemia", "pellagra, mild scurvy and hypochromic anemia", and "iron deficiency anemia with subacute combined sclerosis of the cord."

It is interesting to note that in all of Haden's patients there was anachlorhydria or hypochlorhydria, and that in addition to a well balanced diet rich in vitamins, liver was used in those who improved.

Haden's report of his case of pellagra and pernicious anemia is interesting in that "with high vitamin feeding and liver extract intramuscularly" there was marked improvement in all the symptoms both of pellagra and pernicious anemia. Haden suggests "It is possible that all this patient's difficulties followed the absence of some one factor supplied therapeutically by liver extract." Haden's report of his case of pellagra and pernicious anemia is as follows:

An unmarried woman aged 60 years had been losing weight for three months and had become increasingly weak and mentally dull. The dorsum of the hands showed marked wrinkling and a scaly dermatitis. The basal metabolic rate was minus 35 per cent. The blood examination showed red blood cells, 2 990 000, hemoglobin, 65 per cent (10 Gm.), volume index, 1.21, color index, 1.08, leucocytes, 10 100 with a normal differential count. The temperature ranged from normal to 102° F.

but gradually returned to normal With high vitamin feeding and liver extract intramuscularly the edema disappeared the mental processes became alert and the appearance was much brighter The patient had the macrocytic anemia typical of pernicious anemia as well as the skin and mental changes seen in well developed pellagra The picture is much like that produced by Miller and Rhoads in swine with a black tongue diet It is possible that all this patient's difficulties followed the absence of some one factor supplied therapeutically by liver extract

Of particular importance is Haden's statement that "multiple manifestations may be related to a single deficiency " He cited the experimental work of Miller and Rhoads They said

Using a diet which produces blacktongue in dogs and which was considered by Goldberger to be deficient only in the pellagra preventive factor has produced in swine (1) an anemia usually macrocytic but sometimes microcytic (2) ulcerative lesions of the oral mucous membranes, (3) gastric achlorhydria with the absence of the normal hematopoietic activity of the gastric secretion (4) diarrhea and (5) motor weakness With this diet which contains all mineral salts and known vitamins they have thus produced symptoms suggestive of sprue pellagra and pernicious anemia The symptoms are prevented or cured by liver extracts so these authors conclude that they are due to the lack of some unknown constituent contained in liver extract "

My Case of Pernicious Anemia and Sprue —In 1930 I treated a patient who had both pernicious anemia and sprue and in whom dramatic improvement followed the use of canned liver

Case Report —A man aged 50 years height 5 feet 9½ inches weight 107¾ pounds He complained of sore mouth frequent stools more in mornings and in evenings after supper, weakness and loss of weight Physical examination was negative except that his skin had the lemon yellow tint of pernicious anemia Physical examination was negative Hemoglobin was 55 per cent red blood count 2 570 000 white blood count 7,000 Wassermann was negative Anachlorhydria No blood or parasites were found in several specimens of feces He was a charity patient and could not buy liver extracts and living in the country he could not get fresh liver regularly He was advised to try canned liver He used Armour s liver cheese spread which retails at 10 cents a can and wholesale at one dollar a dozen His neighbors gave him their chicken livers, when they ate chicken

In addition a full diet eliminating corn bread and cane sugar products was prescribed His neighbors also gave him milk to which he added 6 c c of dilute hydrochloric acid to each glass full, with meals and three hours after meals

He returned for re examination in four months when his hemoglobin was 75 per cent and his red blood count 4 250 000 and white blood count 7 200 The stomatitis disappeared his diarrhea had subsided

and his weight had increased to 160 pounds He felt well and was working every day on a little farm A year later his hemoglobin was 85 per cent, red blood count 4,500,000, and white blood count 8,600

Three and a half years later, in 1937, he became careless about his diet and stopped eating the canned liver, when his sore mouth, diarrhea, weakness, and anemia returned At this time he had furuncles on the dorsal surfaces of his hands but the eruption bore no relation to the erythema of pellagra, and he gave no history of any pellagrous skin lesions His hemoglobin had dropped to 38 per cent, his red blood count to 1,500,000 and white blood count to 5,000 He was advised to go back on canned liver and the dietary regimen he had followed in 1930

In this case the use of dilute hydrochloric acid and an improved diet, containing canned liver and a liberal amount of milk, and eliminating corn bread, syrup, and other cane sugar products, relieved the stomatitis and diarrhea of sprue and brought his hemoglobin and red blood count to normal Recrudescence of the symptoms of sprue followed when he discontinued the canned liver and returned to his former dietary habits, and his hemoglobin dropped to 38 per cent and red blood count to 1,500,000 This patient lives some distance from Birmingham and he has not been seen or heard from since his last visit when his low blood count proved the correctness of the diagnosis of pernicious anemia

Haden's Case of Sprue and Pernicious Anemia—Haden, in 1936, reported a case of pernicious anemia and sprue He said that "this patient had a macrocytic anemia due to a deficiency of the antipernicious anemia factor, and the low proteins, the leucocytosis, the diarrhea and the hypocalcemia of sprue With intramuscular liver therapy the appetite returned, the edema began to disappear and before the patient left the hospital the bowel movements decreased to two or three a day with normally formed stools"

Edgar Hines, Jr, called attention to the sometimes difficult differential diagnosis between pellagra and sprue, and expressed the opinion that tropical sprue is not an infrequent disease in South Carolina and that no doubt cases of sprue have been incorrectly diagnosed as pellagra or pernicious anemia

Sydenstricker on the Relation of the Stomach and Liver to Pellagra and Pernicious Anemia—Sydenstricker and Armstrong have had the idea of gastric and hepatic pathology as

possible primary factors in the genesis of pellagra for some time. They discussed in their review of 440 cases of pellagra published in May, 1937, the importance of gastric and liver dysfunction in the etiology of pellagra.

Sydenstricker, predicating the existence of an intrinsic factor in the gastric juice as a factor in pellagra, seems to have shown that impaired function of the stomach, if not a *sine qua non* in the production of pellagra, is at least a factor. Sydenstricker, a clinician of unusual ability, with a flair for original investigations as shown by his work on sickle cell anemia, is impressed with the almost constant pathologic changes in the liver in pellagra—92 per cent in his series of 440 cases.

Added to this evidence of pathologic physiology of the liver and stomach in pellagra is the fact that liver and liver extracts cure pellagra. Deductions drawn from the original investigations of many clinicians led me to suggest that combined liver and gastric pathology or pathologic physiology of both may be essential for the production of pellagra. Thus it appears that there is basis for the assumption of common etiologic factors in producing changes in the liver and stomach which produce in one case pernicious anemia and in another pellagra. This does not mean that I think pernicious anemia and pellagra are different manifestations of the same disease, though I do believe that they are allied nutritional diseases having many symptoms in common and possibly the same etiologic factors, with modifications, may act in the one case to cause pernicious anemia and in another pellagra.

Sydenstricker in discussing the similar findings in cases of pellagra, pernicious anemia and sprue, mentions the difficulty in occasional cases of making a differential diagnosis. He added: "More suggestive than apparent similarity in clinical manifestations is the fact that liver extracts are curative in all three diseases." He also mentioned two of his patients "in whom typical Addisonian anemia developed after repeated attacks of pellagra."

Sydenstricker's originality in research was demonstrated by an experiment in which he showed that an extract made from the fatty liver of an untreated uncomplicated fatal case of pellagra contained the antipernicious anemia fraction but not

the pellagra preventive factor as found in healthy livers This led Sydenstricker to advance the "hypothesis that pellagra might result from intrinsic defect of the liver as well as from extrinsic deficiency"

Sydenstricker concludes as follows

"Pellagra presents many phenomena analogous to pernicious anemia and sprue In pellagra primary vitamin deficiency results, after varying periods of time, in gastric atrophy or dysfunction in failure of liver storage of vitamin compound, in changes in the entire enteric absorptive mechanism, with diarrhea as a symptom"

Petri and his associates (Act med Scandinav 93 375, 1937) in discussing the gastrogenic etiology of pellagra suggest that "in view of the therapeutic efficacy of stomach preparations in pernicious anemia, pellagra and polyneuritis, these diseases may be of uniform etiology, that is, they represent a gastrogenic neurocutaneous syndrome"

Possible Gastric Internal Secretion—In 1927 I called attention to the fact that there is a known internal secretion of the duodenum, secretin, which when changed into prosecretin by the presence of dilute hydrochloric acid stimulates the secretion of trypsinogen and trypsin, amylopsin and steapsinogen and steapsin by the pancreas At that time I also pointed out that secretin, or other internal secretion of the duodenum, is supposed to stimulate liver function

It seems not impossible that the stomach may secrete an internal secretion which stimulates liver function Reasoning a little further, may not the intrinsic gastric factor be an internal secretion which functions synergistically with liver endocrines?

Hunter's Hemolytic Theory of Pernicious Anemia—Murphy, in his recent book on *Pernicious Anemia* (W B Saunders Company, 1939), dismisses the role of infection in the gastrointestinal tract as a factor in the production of pernicious anemia by saying "There is little evidence available to support the theory of toxemia resulting from bacterial activity" He does not even mention the work of William Hunter, who in 1888 announced his theory of oral sepsis, the precursor of gastrointestinal infections, as the primary cause of pernicious anemia Others including myself believe that William Hunter went a long way toward predicating the correct theory of the etiology

of pernicious anemia. Osler particularly was impressed with William Hunter's hypothesis of the genesis of pernicious anemia.

William Hunter found oral infections, particularly glossitis, and gastrointestinal symptoms so constantly present in pernicious anemia that he believed pernicious anemia was a chronic infection due to streptococci and other septic organisms, affecting first the mouth and extending to the stomach and intestines. He believed that toxins formed in the gastrointestinal tract were hemolytic, resulting in the destruction of red blood cells faster than they could be manufactured by the blood forming apparatus. Hunter accounted for the hyperplasia in the bone marrow as being due to a compensatory reticulocytosis. He also believed that the immature cells found in the circulation and in the bone marrow in pernicious anemia are due to the effort of the hematopoietic system to replace the loss of red blood cells destroyed by gastrointestinal toxins.

Whipple, in 1922, opposed Hunter's theory of erythrocytolysis in pernicious anemia, expressing the opinion that it is due to "faulty blood construction and increased disintegration." Since that time, Peabody, Minot and Murphy and others whose investigations have been more in liver therapy than in etiology accept Whipple's hypothesis.

Whether the "antipernicious anemia substance" in liver and liver extracts prevents erythrocytolysis or promotes reticulocytosis is not of great importance so far as controlling pernicious anemia but it seems possible that the "substance" in the liver may be a hormone.

Intestinal Parasites in Pellagra, Sprue, and Pernicious Anemia.—When pellagra was found to be endemic in the South, the campaign to eradicate hookworm was in progress. H. F. Harris, of Georgia, if not the first, was one of the first clinicians to diagnose uncinariasis in the United States. In 1904, two years before pellagra was found to be endemic in Alabama, H. F. Harris demonstrated in his clinic in the College of Physicians and Surgeons in Atlanta a case of hookworm, in which there were symptoms of pellagra. Sandwith reported that the first cases of pellagra recognized in Egypt were in patients who also had hookworm disease. Parish of Texas

found uncinaria in the feces of so many of his pellagra patients that he advanced the theory that pellagra was due to soil polluted with some parasite related to the uncinaria. Undoubtedly pellagra may be secondary to uncinariasis.

Severe types of anemia were found in hookworm patients, some of which could not be diagnosed from pernicious anemia. The anemia in hookworm patients in Porto Rica was an outstanding feature. Colonel Bailey K. Ashford, of the Medical Department of the United States Army, was sent to Porto Rica to study hookworm anemia, and he found that sprue was a more difficult problem than hookworm disease among the inhabitants of that island. Ashford observed that the anemia of 5,000 hookworm patients on the Island of Porto Rica was cured by giving them thymol.

A much discussed question in the early days of the hookworm campaign was whether the parasites in fastening their hooklets to the intestinal mucosa cause minute hemorrhages, which in the aggregate caused the anemia, or whether they excreted a toxin which destroyed red blood cells. The toxin theory seemed more plausible. Severe macrocytic anemia occurs not infrequently in persons infested with the dibothriocephalus tapeworm. It is an interesting coincidence that Norway and Sweden, the only countries in northern Europe in which pellagra is endemic, also have a high rate of bothriocephalus tapeworm infestations associated with severe anemias.

Murphy cites Becker as having reported 18 cases of severe macrocytic anemia in patients infested with the bothriocephalatus, and that treatment with liver and liver extracts, without the expulsion of the worm, cured the anemia. This would suggest that liver insufficiency is the cause of the anemia in the bothriocephalus tapeworm. Liver and liver extract would seem to be replacement therapy in such cases.

The fact that a lipoid substance obtained from segments of the bothriocephalatus tapeworm will cause hemolysis suggests that in individuals infested with the short tapeworm the toxin is liberated in the intestinal tract and carried to the liver, there producing damage to the extent of causing liver insufficiency. The fact that the use of liver extract overcomes the anemia

even when the worm has not been expelled further suggests that the liver insufficiency is the cause of the anemia

Alcoholic Pellagra, Cirrhosis of the Liver, and Pernicious Anemia—Alcoholism is a known cause of pellagra, in which pathologic changes in the stomach and liver may be assumed, and the fact that pernicious anemia is frequent in alcoholic cirrhosis of the liver, would suggest that liver insufficiency may occur in alcoholics who develop pellagra or pernicious anemia

M D Van Duyn 2nd, in an article on "Macrocytic Anemia in Disease of the Liver" reported a case of pernicious anemia in a patient who had cirrhosis of the liver He made a careful study of the literature to determine whether or not in such cases "macrocytic anemia is secondary to, or independent of, hepatic cirrhosis, and if the presence of macrocytic anemia might not be an indication of disease of the liver?"

Van Duyn found a number of references in the literature to the association of macrocytic anemia with cirrhosis of the liver In searching hospital records of the institution with which he is affiliated, he found that in 28 cases of cirrhosis of the liver, 5, or 18 per cent, also had macrocytic anemia

William B Murphy in his recent very readable book on *Anemia in Practice and Pernicious Anemia* (W B Saunders Company, 1939), in discussing the cirrhosis of the liver associated with macrocytic anemia seems to associate "liver damage to the storage of sufficient antipernicious anemia substance normally stored in the liver to hinder normal hematopoiesis" He adds The presence of some degree of cirrhosis of the liver is not uncommon in patients of the older age groups with pernicious anemia In this group response to antipernicious anemia substance is likely to be slow because of the associated cirrhosis Because of the slow and unsatisfactory response, one may be led to the conclusion that the cirrhosis is the primary disturbance rather than a complication of true pernicious anemia"

Spies' Observations on Pellagra, Sprue, and Pernicious Anemia—Spies and Payne seem to have proved that pellagra and pernicious anemia are different diseases They removed achylic gastric juice from the stomachs of two acute cases of pellagra on diets free from the pellagra preventive factor They incu

bated the gastric juice with beef and gave it to two pernicious anemia patients A characteristic reticulocyte response showed the presence of Castle's intrinsic factor The beef incubated with the gastric juice of pellagrins did not affect the course of the pellagra

Williams and Spies say that "the peripheral neuritis in patients with pernicious anemia cannot be distinguished pathologically from the peripheral neuritis associated with pellagra" They also state that "the peripheral neuritis of tropical and non tropical sprue is clinically indistinguishable from that of beriberi, pellagra or pernicious anemia" I would add that while I believe pellagra, sprue, and pernicious anemia are different diseases, it is an interesting fact that peripheral neuritis occurs in all three conditions

Spies said "It is my impression that pellagra, sprue, and other similar conditions are probably closely related in that their development may be dependent on an inadequate food intake, or assimilation"

J S McLester in the last edition of his book on *Nutrition and Diet in Health and Disease* expressed the opinion that "sprue is a deficiency disease similar in nature to pernicious anemia and pellagra"

Conclusions

1 Pellagra, pernicious anemia, and sprue are distinct and separate disease entities

2 The *mouth and gastrointestinal symptoms in pellagra,* without skin lesions, pernicious anemia, and sprue may be in*distinguishable one from the other in cases in which there is* macrocytic anemia

3 The most effective treatment in pellagra, pernicious anemia, and sprue is liver and liver extracts Nicotinic acid is an ingredient of liver and liver extract

4 Liver pathology, usually fatty degeneration, is an almost constant finding in pellagra and pernicious anemia and to a less extent in sprue *Atrophy of the stomach and intestines* may be found in all three diseases If cord changes are found in pellagra, pernicious anemia, or sprue, the lateral and posterior columns are involved

5 Liver insufficiency appears to be a factor in the genesis of pellagra, pernicious anemia, and sprue

6 The hypothesis of liver endocrines as controlling erythrocytolysis is discussed

7 Greenspon's and Roger Morris' suggestion of a gastric hormone as the intrinsic factor in preventing pernicious anemia is discussed The interrelations and the similarity of vitamins and hormones are discussed

8 Cases are reported, and collected, in which pellagra and pernicious anemia, sprue and pernicious anemia, pellagra, sprue and pernicious anemia existed in the same patients This fact suggests common etiologic factors

9 The frequency of intestinal parasites in anemic patients who have pellagra, pernicious anemia, or sprue is mentioned with the suggestion that intestinal toxemia and liver insufficiency may be etiologic factors in some cases

10 Sydenstricker's views on the relation of the stomach and liver to pellagra and pernicious anemia are discussed

11 The occurrence of pellagra in alcoholics, and the not infrequent complication of pernicious anemia in cirrhosis of the liver, suggest that liver pathology and, or, liver insufficiency, may be factors in alcoholic pellagra and pernicious anemia in patients who have cirrhosis of the liver

12 Pellagra, pernicious anemia, and sprue appear to be allied nutritional diseases

CHAPTER XIV

PATHOLOGY

Mouth.—The pathologic changes in the mouth in pellagra are variable, depending upon the severity of the case and the length of time the disease has existed. In the early stages of mild cases, there is a fiery red tongue and hyperemia with redness of the mucous membrane of the entire oral cavity. In some cases there are aphthous patches on the buccal mucous membrane and gums, and the tongue may be thick and heavily coated with red glazed margins. As the disease progresses, in the neglected and fatal cases, fibrotic changes occur, particularly of the tongue. It becomes smaller, the mucous membrane sheds, and the entire tongue is glazed or deeply fissured and of dark red color, sometimes resembling rare beef. Microscopic section shows a marked increase in fibrous tissue throughout the submucosa and in the deeper structure of the tongue. There may be deep ulcerations covered with thick dark pus due to secondary infections.

The fauces are usually hyperemic in the early stages and in the old and fatal cases fibrous changes occur in the submucosa. Ulcerations of secondary pyogenic character may be found in the pharynx.

Esophagus.—The esophagus shows evidence of chronic inflammatory changes, sometimes with secondary ulceration.

Stomach.—The stomach shows no characteristic changes except that usually there is thinning of the walls of the stomach with atrophy of the glandular tissue. Fibrotic changes in the stomach are found in the chronic cases that go to autopsy. In the typhoid or fulminating type, the stomach is hyperemic, covered with mucus, and sometimes there is superficial ulceration near the pylorus.

Intestines, Colon, and Rectum.—Kenneth Lynch, Professor of Pathology in the Medical College of the State of South Carolina, in 1916, performed autopsies on and made noteworthy

pathologic studies of the intestines in 32 pellagrins, ranging in age from childhood to old age He found constant morbid changes in pellagra in the large intestine The following excerpts from Lynch's paper describe the pathologic changes which he regards as characteristic of pellagra

'The characteristic change which has occurred most distinctly in the subacute cases is practically limited to the large intestine, the cecum sigmoid and rectum being its particular seats The cecum may be large but the remainder of the large gut is commonly contracted The mucosa is somewhat swollen but firm and rather smooth out on the surface The inner surface is often hyperemic and commonly of a deep red color this color being most marked in the cecum sigmoid and rectum The wall as a whole is usually thickened

'Microscopically the outer coat shows a fibrosis which may be of minor or marked degree It is commonly of distinctly progressive proportions, showing more cells than the normal In the muscular coat there is an infiltration with lymphocytes and an overgrowth of connective tissue between the bundles of muscle This feature varies and the muscle may be of normal proportions or considerably atrophied and replaced In some cases the cecum sigmoid and rectum are the only parts involved in some only one of these parts is affected and in others the involvement of the large intestine is general In the chronic case there may be atrophy of the intestine in keeping with the general emaciation and in the acute there may be an added acute catarrh showing no distinctive feature

Liver—Pathologic changes in the liver of autopsied pellagrins are almost constant though not characteristic The gross pathology of the liver is variable It may be smaller than normal and show evidences of atrophy, though in some cases there is enlargement with hypertrophic changes The edges of the liver are usually sharply defined, and the capsule may be wrinkled and adherent to the surface of the liver The gall bladder may appear normal, or it may be chronically inflamed and adherent to the duodenum and other adjacent viscera

Microscopic sections of the liver in pellagra, in the great majority of cases, show degenerative changes in the liver cells, usually cloudy swelling with fatty degeneration or there may be brown atrophy of the liver cells Cirrhotic changes may be found particularly in alcoholic pellagra

In 1927 I advanced the hypothesis that hepatic insufficiency, usually as the result of liver pathology, is the underlying factor in the etiology of pernicious anemia and pellagra I then called

attention to the well-known fact that pathology, usually fatty degeneration, of the liver was an almost constant finding in autopsies on victims of pernicious anemia In reviewing the literature on the pathology of pellagra, I likewise have been impressed with the reports by many capable pathologists of almost the same constant changes in the liver on autopsied pellagrins

A thorough study of the pathology of pellagra was made by Pothier, Professor of Pathology at Tulane University In a large series of autopsies on pellagrins in Charity Hospital, New Orleans, Pothier found constant, though variable, changes in the liver He said

"The liver in all the autopsies presented on section a yellow color at times mottled suggesting nutmeg liver The microscopical section shows marked hyperemia, the blood vessels being filled with blood The liver cells are granular, do not stain well, and in many areas have totally disappeared, leaving a reticulated appearance with masses of blood corpuscles In other areas the cells are completely fatty These changes are more marked at the periphery of the lobules The connective tissue (of the liver) in specimens examined show hyperplasia"

The Illinois Pellagra Commission on Liver Pathology in Pellagra—The findings of the Illinois Pellagra Commission in 1912 pointed strongly to the liver as the one organ in which there are constant pathologic changes in pellagra This commission of experts also expressed the opinion that the damage to the liver was secondary to gastrointestinal infections Considering the thoroughness with which the investigations of the Illinois Pellagra Commission were made, and the ability and attainments of the men who made up the commission, it seems strange that pathologic studies of the liver in pellagra have been neglected in the 28 years since that report was published

The Illinois Pellagra Commission in its comprehensive report, entitled "Pellagra in Illinois," discussing pathologic findings, said

"While it cannot be said that there is anything specific about the changes found, yet there are certain features which seem to be constant and open up certain more or less definite lines for future research

"*The liver has been constantly the seat of small islets of low grade inflammation of the portal connective tissue lying in the interlobular septa The intralobular capillaries are engorged and in most cases there*

are many small blood extravasations The liver cells have undergone fatty degeneration which is in some instances remarkable and the change is distributed in every case along the periphery of the lobule This, in the absence of any marked cirrhosis at once suggests that there may have been some toxin circulating in the portal blood stream Some of the specimens even suggest a picture of a very early stage of acute yellow atrophy or the more acute forms of alcoholic cirrhosis

Intestinal ulceration has been present in three out of seven cases This has not the acuity of an amebic infection and no amebas have been found in the walls Even where no ulceration was found a low grade infiltration of the mucosa and submucosa has been present in places These findings are certainly of interest in relation to the condition of the liver

'*All these appearances suggest the presence of some toxic substance in the blood One may go even further and from the changes in the intestine and especially in the liver suspect that this toxin originates in the intestine and enters the circulation by way of the portal system The great frequency of gastrointestinal symptoms during the clinical course of the disease might be regarded as pointing in the same direction* There is always however to be borne in mind the possibility that these changes may be secondary to the pellagra That is to say, that as the result of the gross disturbance in metabolism and vital resistance, which certainly accompany the disease, there may follow a secondary invasion of the intestinal tract with organisms which then give rise to the changes found by virtue of the toxins elaborated during their growth Secondary changes such as this would be quite in accordance with what is found in other diseases

' If however we look for evidences of the localization of a blood borne parasite in other parts of the body we find entirely negative results The picture presented is much more that of a diffuse toxic state than of one due to a blood infection *The only tissues in which there seemed to be any focalization of lesion were in the intestinal wall and the liver In this latter organ the areas of infiltration present in the interlobular septa were decidedly local and often widely separated and where found existed in the form of more or less circular islets There was no generalized invasion of the whole of the connective tissue The intensity of the infiltration was certainly of low grade and did not suggest a very acute inflammation* ''

John Sandwall in summarizing the findings by the Pellagra Commission of the State of Illinois said

The liver is the constant seat of low grade inflammation of portal connective tissue lying in the interlobular septa the intralobular capillaries are gorged and in most cases there are many small blood extravasations and there is peripheral fatty degeneration Evidently some toxic substances originating from the gastrointestinal tract are in the blood these pathologic changes may be secondary to pellagra that is as a result of metabolic disturbance invasion of other agencies from gastro intestinal tract

Sydenstricker and Armstrong in recent studies are impressed with the importance of the pathology found in the liver of pellagrins, particularly as related to gastrointestinal dysfunction They said

"Lesions of the liver, most often fatty degeneration are present in a great majority of the patients coming to necropsy (92 per cent of our small series) It seems likely *that they may have great importance as* part of a picture of gastrointestinal failure That the changes in the gastrointestinal function are primary and causative rather than secondary to pellagra is an attractive hypothesis *Further, it seems probable* that these changes result in an intrinsic deficiency analogous to but probably distinct from that which is present in pernicious anemia "

H F Harris in his monograph on pellagra, discussing the pathology of the liver, said

"It is much to the credit of Morelli that he insisted on the importance of the lesions of the liver, which he thought occurred more frequently than alterations of any of the other organs Out of thirty seven autopsies he found changes in this viscus thirty one times

"Chiarugi found the liver yellow in twenty nine examinations, and Verga noted cirrhosis in two instances

"Lombroso says lesions of the viscus are frequent, he having found the organ diminished in size eighteen times in thirty nine necropsies, and *in eight the gland presented the so called brown atrophy* In twenty seven cases the viscus was yellow and friable

"Carraroli has found degeneration of the parenchyma, with fatty *changes and atrophy, the beam work may be somewhat infiltrated, and* its characteristic structure deformed or lost

"Kozowsky found in the liver cells quantities of brown pigment, with fatty infiltration and degeneration *In some cases albuminoid degeneration, and increase in interlobular connective tissue occurred* The liver cells are sometimes atrophied by the pressure of the surrounding fibrous tissue or by the dilated veins

"In six necropsies by H F Harris the liver was found small in every instance and its consistence somewhat increased in all the viscera presented in a more or less *characteristic fashion the appearances observed* in brown atrophy Microscopic examination showed increase of pigments, dilatation of the central veins of the lobules venous congestion, and here and there *a very slight increase in the interlobular connective* tissue "

Pathology of the Liver in Blacktongue in Dogs —The pathology found in the liver in experimental "blacktongue" in dogs shows histologic changes similar to those found in the liver in autopsies on pellagrins In Bulletin No 162 of the National Institute of Health, United States Public Health Service, Sep

tember, 1933 Lillie in discussing experimental blacktongue in dogs said

"Histologically the liver quite commonly shows slight to moderate congestion of the centers of the lobules sometimes with moderate central atrophy of the cell cords Many cases show no fat in the liver cells others show more or less fatty infiltration usually of the centers of the lobules occasionally more about the portal areas In this fatty infiltration the liver cells contain fine to medium fat droplets in most of the cases coarse droplets in a few Only in one liver was this fatty change of the parenchyma cells as generally distributed as in the yellow liver condition described by Sebrell and the writer, and even in this case the intensity of it was not sufficient to give the characteristic gross yellow coloration This case however may represent a combined picture of the two conditions

"Lipoid droplets were noted in the basal portion of the epithelium of the larger and even smaller bile ducts but as these are seen also in normal and overfed dogs little significance is to be attached to them"

Sebrell's Disease—Sebrell produced a disease in dogs which he called "yellow liver," by feeding them diets containing a sufficient quantity of the pellagra preventive factor but deficient in riboflavin In discussing the possible relationship of yellow liver to blacktongue in dogs and human pellagra Sebrell said

"In 1929 Sebrell made a preliminary report on the occurrence of extensive fatty changes in the liver noted at autopsy in dogs on four different diets The condition was first observed by Goldberger and his associates in the course of experiments designed to test the black tongue and pellagra preventive value of various foodstuffs The occurrence of black tongue in these experiments has been reported A clinical description of blacktongue as observed in his laboratory and its relationship to pellagra has been discussed by Goldberger and his associates The possible relationship of 'yellow liver' to human pellagra is suggested by the fact that the finding of a yellow liver at autopsy in pellagrins is not uncommon Harris quotes several of the older writers on pellagra among them Morelli Lombroso, and Kozowsky as finding either fatty changes or a yellow and friable fatty infiltration of the liver in 3 out of 12 autopsies and Crutchfield found fatty degeneration of the liver in 10 cases which came to autopsy

Lillie and Sebrell in discussing the pathology of "yellow liver" of dogs (National Institute of Health Bulletin No 162, United States Public Health September, 1933) said

"The condition herein described and designated by Goldberger as yellow liver was first seen by him with us in August 1928 That so

striking a gross post mortem finding as the yellow liver *from* which the condition has been named could have escaped notice appears highly improbable, hence the condition is believed to be new Dietary, clinical, and gross post mortem data in this disease have been reported, by Sebrell (1929) "

Lillie and Sebrell in reporting the changes found in the liver of dogs in riboflavin deficiency said

"The liver was regularly yellow in color, with more or less distinct fine red lobular markings The organ was firm, usually quite friable and often distinctly greasy to the feel Usually there was no evident enlargement The same yellow color and fine red markings were evident on the cut section Microscopically the liver cells throughout the lobule were seen toward the centers of the lobules sometimes the reverse was true Generally, the periphery of the lobules was more densely packed with fine fat droplets sometimes the fat deposition was denser in the intermediate or central zones In 5 of the 23 cases more or less numerous large vacuoles containing no fat were seen in the liver cells near the centers of the lobules The epithelium of the larger bile ducts sometimes contained perinuclear fat droplets in the basal two thirds of the cells This finding is seen also in black tongue and in normal dogs (Rosenthal and Lillie 1931)

"It would seem that the fatty change in the liver cells due to the syndrome under consideration is probably primarily periportal in location, and may be combined with the coarse droplet central fatty infiltration seen in dogs in other conditions However the central hydropic degeneration would possibly indicate that the central large droplet infiltration might also be degenerative "

Liver Insufficiency in Ariboflavinosis —Sebrell has identified a disease in human beings due to riboflavin deficiency resembling, and sometimes associated with, pellagra in which there is stomatitis, with cracks or fissures, sometimes "ugly moist sores, in the corners of the lips" Associated with the marginal stomatitis are erythematous, greasy exfoliating areas of skin on and around the nose and on the ears Sebrell first found this condition in the South, and since then a number of cases have been found in Bellevue Hospital New York Sydenstricker has observed a number of cases of riboflavin deficiency in the University Hospital, Augusta, Georgia Spies has reported cases of ariboflavinosis in which eye manifestations are pronounced The symptoms of this new disease do not clear up with the use of nicotinic acid, but small doses of riboflavin cure the marginal stomatitis, also called cheilitis, the skin lesions around the nose and on the ears, and the keratitis and corneal ulcers associated with riboflavin deficiency

Since definite liver pathology is so constantly associated with Sebrell's disease, which he calls ariboflavinosis, it is not difficult to believe that the liver has been damaged to the extent that it is incapable of storing up riboflavin

Since nicotinic acid deficiency and riboflavin deficiency are so closely allied, it appears possible that liver pathology with hepatic insufficiency may be an essential factor in the genesis of both pellagra and ariboflavinosis

Skin—H F Harris has given the best description of the skin pathology of pellagra that has appeared in medical literature He said

> The erythema begins on the back of the hands, and at the bases of the fingers It is at first a livid red and after a few days becomes covered with scales and shed off epithelium this hyperkeratosis continues throughout the course of the eruption, and is exceedingly characteristic The tissues are swollen as a consequence of the increase of both blood and serum in the derma and as a result the normal elevations and depressions of the skin become more marked than usual, giving to the back of the hand a wrinkled appearance, the contrast between the youthful face and the aged characteristics of the hand are most striking in some subjects This lesion extends gradually until in most cases it covers the entire backs of the hands and may reach up to a greater or less height along the forearm and even to the shoulders It does not often extend to the tips of the fingers but may do so After several recurrences the backs of the hands become pigmented and in some cases the skin becomes permanently thinned
>
> "Similar lesions are observed on the backs of the feet though by no means so common as in the location already described they always occur with or following the eruption of the hands The erythema may spread to the ankles and legs
>
> " In quite a number of cases the lesion is observed on the face, beginning usually on the bridge of the nose and gradually extending over its entire surface down on the cheeks and in extreme instances may reach to the chin and lips and spread itself finally over the entire countenance It is more frequent in men than women The scalp remains normal The eruption may be in small distinct spots though it is usually confluent In some cases it occurs also on the neck to the so called 'Casal's necktie
>
> "More rarely still other parts of the body may be affected the change being observed on the elbows on the arm and on the skin covering the popliteal space on the scrotum around the anus and in the perineal region In women the vagina may be inflamed and later ulcerated In a rapidly fatal case in a white man following the eruption on the hands I recently observed spots scattered over the various parts of the body of an irregular form sharply circumscribed and pigmented to such a degree that they appeared almost black, they were not preceded by an erythema "

Heart—Porter and Higginbotham studied the heart in endemic pellagra. The absence of gross pathology of the heart in pellagra as compared to the hypertrophy found in beriberi was striking. The average weight of 14 hearts from patients dying with pellagra was 307 Gm. for males and 255 Gm. for females. They cite White as estimating the normal weight of the heart as 300 Gm. for males and 250 Gm. for females. These authors confirm the findings of Lombroso who weighed the hearts of 26 pellagrins. In only two did the weight of the heart exceed the average normal, 5 weighed slightly less than normal and the remainder showed marked decrease in weight.

Pothier, of New Orleans, who performed a large number of *autopsies on pellagrins found that "in the majority of cases the* heart both grossly and microscopically did not present many changes."

Lungs—The lungs have been found to be normal in most of the reported autopsies on pellagrins. The rarity of tuberculosis in pellagrins has been commented upon, though in a small proportion of cases pulmonary tuberculosis coexists with, or is a complication of, pellagra.

Kidneys—The kidneys in dead pellagrins have been found to be normal, or they present the atrophic and degenerative changes usually found in chronic wasting diseases.

Nervous System—The pathology of the nervous system in pellagra seems to have been neglected, because medical literature records but few reports of anything like a comprehensive study of the changes in the brain, cord, ganglia, and peripheral nerves in large series of autopsies. The consensus of opinion among those who have made pathologic studies of the nervous system in pellagra seems to be that the most frequent picture is that of a subacute combined sclerosis. There may be inconstant degenerative changes in the brain, but the most conspicuous pathology in pellagra is in the posterior columns of the cord, with peripheral degeneration of the nerve fibers.

Beverly Tucker reported pathologic studies of 2 brains, 6 cords, and 2 ganglionic chains. He said: "Pellagra was found to affect the brain but slightly, the cords diffusely, especially in the cervical and lumbar enlargements, and spinal sympathetic ganglionic changes extensively." Tucker's pathologic investi-

gations and his clinical studies convinced him that pellagra is primarily a disease of the nervous system, due probably to a filtrable virus like poliomyelitis Tucker cites H F Harris as having found changes in the sympathetic ganglia and Langworthy as having found "marked pigmentary changes in the cells of the autonomic and sensory ganglia in one case" Tucker also cites Mott as having found "scattered degeneration throughout the white matter of the cord more marked in the posteromedium columns of the cord with swelling of the posterior ganglia"

The most comprehensive article on the pathology of the nervous system in pellagra that has appeared in American medical literature was published by H F Harris (South M J 5 75, 1912)

SECTION IV

CLINICAL INVESTIGATIONS

CHAPTER XV

STUDIES ON PELLAGRA AT THE DUKE UNIVERSITY SCHOOL OF MEDICINE

By Julian M Ruffin, M D, Associate Professor of Medicine, and David T Smith, M D, Associate Professor of Medicine, Durham, N C

Introduction

At the time of the opening of Duke Hospital in 1930, there were many aspects of pellagra upon which students of the disease had been unable to agree The chief controversial issues were (1) the etiology of the disease, (2) the relationship of its symptomatology to exposure to sunshine, and (3) the most effective form of therapy With the exception of the spectacular studies by Goldberger, Wheeler, and their associates[38 40 41 42 44 129] there had been little, if any, carefully controlled work on the subject Although it was agreed generally that a deficient diet was an important factor in its etiology, there were many physicians who felt that infection played a prominent role, or at least that a deficient diet was not the whole story[65 117 120]

In an effort to answer these questions, an intensive study of pellagra was begun at Duke Hospital in 1931 and has continued up to the present time

Material —Since the opening of the hospital, 465 patients suffering from pellagra have been observed The incidence according to race, sex, and age is shown in Tables V and VI Two hundred and twenty eight of these patients were treated in the Out Patient Clinic and the remaining 237 were hospitalized

Method of Study —Realizing that most patients having pellagra tend to recover when admitted to a hospital and fed a well balanced diet, it was decided to feed those patients who

TABLE V

DISTRIBUTION OF CASES

	WHITE	COLORED	TOTAL
Male	133	16	149
Female	261	55	316
			465

TABLE VI

INCIDENCE ACCORDING TO AGE

AGE	NO. OF CASES	PERCENTAGE
0–9	19	4
10–19	29	6
20–29	96	21
30–39	111	24
40–49	96	21
50–59	56	12
60–69	51	11
70–79	7	1
Total	465	100

were selected for study a deficient diet, similar to that which they had been consuming at the time of the appearance of the disease. This was called the standard basic diet No. 1 (Table VII) and was especially deficient in the vitamin B complex. It was supplemented by other known vitamins and minerals to make it deficient in the pellagra preventive factor only.

Selection of Patients.—All patients reported in this study had the characteristic dermatitis over the exposed parts of the body (Figs. 11, 12, and 13) and one or more constitutional symptoms of the disease, such as glossitis, anorexia, diarrhea, nausea, vomiting, abdominal pain, or mental disturbances. Nervousness and irritability were common, and actual psychoses frequently were encountered.

Early Observations.—It soon became apparent that the rash in certain of the patients who had clinically active pellagra improved while they were eating the deficient diet. It was also observed that some of these patients became generally worse, although the rash had subsided. Similar observations were made by Spies.[101]

It was discovered and reported in 1932[9] that exposure of an arm or leg to the direct rays of the sun may result in a recurrence of the dermatitis, accompanied by an exacerbation of con-

TABLE VII

STANDARD BASIC DIET NO 1

ARTICLE	QUANTITY (GM)	PROTEIN (GM)	FAT (GM)	CARBOHYDRATE (GM)	MINERALS (GM) CALCIUM	PHOSPHORUS	IRON	VITAMINS A	B	C	D	G	CALORIES
Corn meal	92	8 3	2 0	69 0	0 0110	0 1225	0 0006		±			±	2890 0 (Corn meal to Fat salt pork)
Cane syrup	105			89 2					+			+	
Flour	111	12 5	1 2	83 4	0 0220	0 1030	0 0010		+			−	
Lard	81		81 0										
Rice	25	2 0	0 1	19 6	0 0023	0 0240	0 0002						
Field peas	90	19 2	1 4	54 6	0 0756	0 0760	0 0052	+	+			+	
Hominy grits	51	4 3	0 3	40 6	0 0056	0 0734	0 0005	+	+			+	
Fat salt pork	60	1 1	51 3	0 0	0 0011	0 0115	0 0001						
Cod liver oil	90 c c		90 0			0 0117		+++			+++	+	810 0
Tomato juice	45 c c	0 4	0 1	2 0	0 0050		0 0002	+	+	+++		+	10 3
Iron ammonium citrate	6						1 0200						
Calcium gluconate	6				0 5580								
Cheese	60	17 4	21 6		0 5586	0 4098	0 0007	+	+				264 0
Total		65 2	249 0	358 4	1 2392	0 8319	1 0285	+++	++	+++	+++	+	3974 3

stitutional symptoms. Furthermore, it was found that when the deficient diet consumed by the patient was supplemented by extracts of whole liver in doses of 90 c c daily, exposure to sunshine produced no reaction whatever, except for a normal healthy tan. This simple procedure afforded a satisfactory criterion of recovery from the disease, and has been employed subsequently throughout all of our studies.



Fig 11.—Typical rash over the dorsum of the hands. Note the deep fissures between the heavy crusts.

Effect of Sunlight on the Clinical Manifestations of Pellagra

Historical.—For nearly two hundred years the influence of the sun's rays on the lesions of pellagra has been a subject of debate. One of the common names in Italy applied to this disease by the peasants is *mal del sole* (disease of the sun), while certain Italian physicians have described the lesions as "sun stroke of the skin."[84] Many modern clinicians[3, 8, 18, 19, 4, 49, 5, 6, 6, 1, 7, 80, 82, 114, 118, 128, 1, 1, 131] believe that there is a close relationship between exposure to sunlight and the development of cutaneous lesions in a pellagrin, and certain observers[3, 4, 4, 6, 80, 83, 94, 130] have produced typical cutaneous lesions in pellagrins by exposing normal or recently healed areas of skin to direct sunlight. Because lesions occur on unexposed portions



Fig 12—Collar of Casal Note fissures at corners of the mouth

of the body, such as the elbows, knees, sacrum scrotum, and perineum, other students [1, 27, 8, 103, 119, 14] of pellagra deny the influence of sunlight in the production of the dermatitis In an effort to determine which of these conflicting views was correct, the following studies were undertaken

Clinical Observations—On reviewing the histories it was noted that a majority of patients having pellagra, when specifically questioned, recalled a prolonged exposure to sunlight shortly before the cutaneous lesions developed, and that the



Fig 13—Lesions on feet with usual exfoliation of skin

appearance of the dermatitis was almost invariably followed by constitutional symptoms of varying intensity The clinical impression that exposure to sunlight may cause the dermatitis was further supported by the spontaneous development of asymmetrical and bizarre lesions which were observed in 10 patients in this series (Figs 14, 15, and 16) These findings suggested that the dermatitis usually seen over the exposed surfaces of the body is due to the action of sunlight and that the constitutional manifestations of the disease are in some way related to

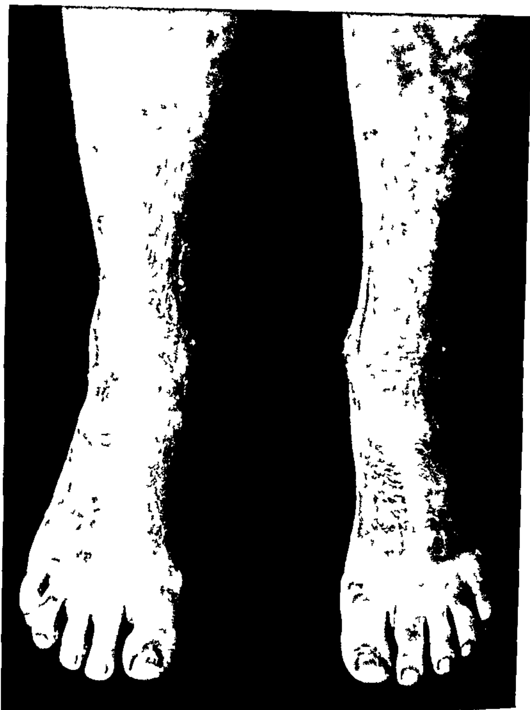


Fig 14—Dermatitis showing pattern of the shoes in a patient having typical pellagra



Fig 16—An unusual location of the dermatitis This girl had been bending over working in a field She had the typical dermatitis on the hands al o

apparently normal skin which had been protected by clothing. In these, one usually observed a marked erythema with the formation of large vesicles, such as one observes in a burn from boiling water. In one patient a crusty, weeping lesion developed over an area of previously normal skin (Fig 17). Two patients in whom no dermatitis was observed showed an accentuation of constitutional symptoms following exposure to sunshine.

The condition of the tongue became definitely worse after exposure to sunshine in 27 of the 36 patients. Exposure was followed by an increase in the diarrhea and anorexia in 21 patients. Nausea and vomiting developed in 10 and dementia in



Fig 17.—Dermatitis following experimental exposure of one arm. The other arm remained entirely normal. (After Ruffin and Smith, Am J M Sc 187 512, 1934.)

4 In all the 36 patients, one or more severe constitutional symptoms developed after exposure to direct sunlight. Neither cutaneous lesions nor general symptoms occurred in any of these 36 patients after re-exposure to maximum doses of sunlight following adequate treatment.

In the remaining 45 patients, exposure to sunshine resulted in no local reaction or increase in the general symptoms. All of this group recovered completely while subsisting upon the deficient diet.

Explanation for Failure of Pellagrins to Relapse After Exposure to Sunlight.—A satisfactory explanation for the recov



—Experimental exposure of one leg Note marked erythema and large vesicles on foot

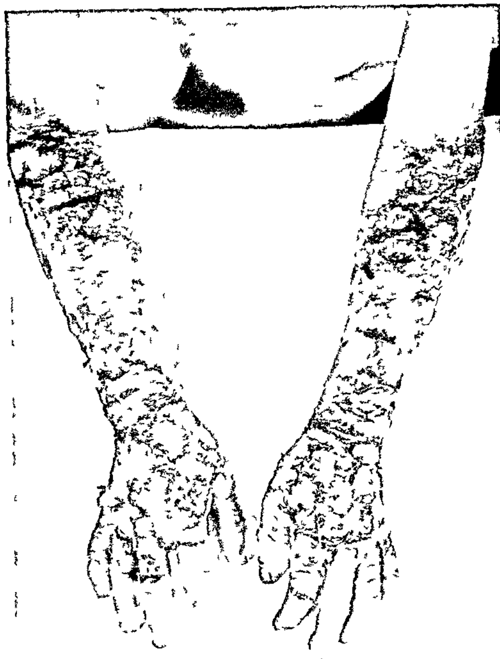


Fig 19—Lesions on hands and forearms in an old neglected case of *pellagra* White woman aged 52 years Note the thickened indurated tissue with pigmentation in the fissures Riboflavin had no effect but the skin lesions cleared up with the use of Valentine's whole liver extract

ery of these patients who were subsisting upon the deficient diet is difficult to offer Similar recoveries have been reported by Matthews[70] and by Sydenstricker and his associates[115] The following observations may afford an explanation for the observed facts (1) It was learned that, in some instances, the patient had eaten yeast, liver, red meat, or fish after the lesions appeared and shortly before admission to the hospital, (2) the basic diet is not entirely free of the pellagra preventive factor and in general is a much better diet than that eaten by the patient at home, (3) the maximum period of exposure to sunlight was only two hours per day in contrast to the eight to ten hours to which the patient was frequently subjected before entering the hospital, and (4) our patients were in bed, were less active than before admission, and therefore might not need as much of the pellagra-preventive factor as an ambulatory patient

Effect of Exposure to Heat —The development of dermatitis in pellagrins after exposure to heat from a stove has been reported by Niles[5] and Bass[3] In three of our patients typical pellagra with severe constitutional symptoms followed exposure of the hands to a red hot stove These observations suggest that the acute manifestations of pellagra in a susceptible individual may be precipitated by exposure to heat

In 4 cases, studied experimentally, cutaneous lesions and associated constitutional symptoms developed after exposure of the hands to the rays of an electric heater After adequate dietary treatment, the patients were re exposed to three times the original amount of heat without the development of either cutaneous lesions or general symptoms In contrast to these results with red and infrared rays, various observers[4, 0, 45, 103] have failed to produce any reaction in pellagrins following exposure to ultra violet light

Possible Relationship of Porphyrins to Dermatitis —There is no satisfactory explanation for the deleterious effect of sunlight on the pellagrin The acute inflammation of the skin, gastro intestinal disturbances, and dementia resemble some of the symptoms of acute porphyrin intoxication, which is also pro

duced by exposure to the direct rays of the sun. Hausmann[51] suggested many years ago that accumulation of porphyrins in the pellagrin might explain his sensitivity to sunlight. Fischer,[3] in 1916, and Kammerer and Weisbecker,[4] in 1933, found that coproporphyrin would sensitize animals to light but gave less violent reactions than uroporphyrin. Until recently no accurate methods were available for measuring porphyrin excretion in pellagrins. Beckh, Ellinger, and Spies[6] modified Thiel's calorometric method and studied the porphyrin excretion in a large series of pellagrins. It is evident from later studies that they were not measuring porphyrins alone but included other colored substances in the urine. Watson[125, 1 6, 12] and Dobriner, Strain and Localio[3] devised more accurate methods for measuring coproporphyrin I and Dobriner,[4] and his associates measured carefully the daily excretion of coproporphyrin in the urine and stools of a pellagrin before and after treatment with liver extract and yeast. Coproporphyrin I was increased in both the urine and the feces before treatment and decreased with clinical improvement. Similar but less marked differences in the urinary coproporphyrin have been observed in treated and untreated pellagrins at Duke University by McAnally, Smith and Perlzweig.[63] It is tempting to offer this evidence of increase of coproporphyrin as an explanation for the pellagrin's sensitivity to sunlight, but a similar increase occurs in lead poisoning and in certain cirrhoses of the liver,[13] in arsenical dermatitis, and in poisoning with cinchophen, sulfonal, and trional[1 6] and may therefore be a result rather than a cause of the disordered metabolism in pellagra.

Necessity for Producing Relapse Before Evaluation of Curative Substances.—In the group of 45 patients in whom no relapse was observed after exposure to sunlight, any attempt to test the efficacy of a curative substance obviously would have been futile. This emphasizes the importance of producing an accentuation of symptoms as a prerequisite to the evaluation of any curative substance. The failure to take this fact into consideration probably accounts for the voluminous literature which has accumulated on therapy, and the numerous unrelated substances which have been reported as specific cures for pellagra.

Types of Skin Lesions—The *cutaneous* lesions whic
produced experimentally by exposure to direct sunligh
identical in most instances with the spontaneously occ
lesions first described by *Casal*[14] In addition to this
dermatitis which appears on the exposed surfaces, patien

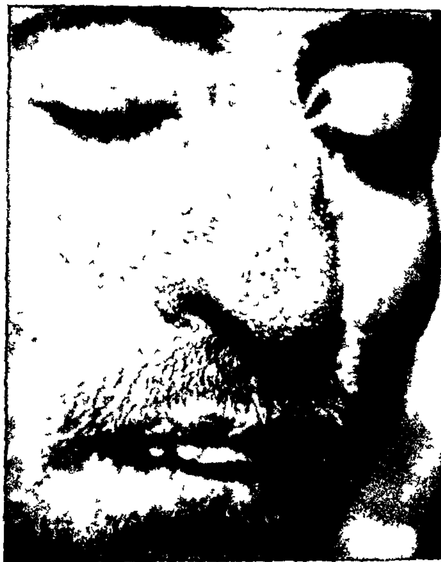


Fig 20—Seborrhea on the nose frequently seen in pellagra

present (1) seborrhea over the face and neck (Fig 20)
hyperkeratoses with increased pigmentation over the
prominences of the body (Fig 21), and (3) lesions abou
genitalia (Fig 22) The seborrhea usually occurs about
alae nasi but at times over the forehead face and neck

yellow material. This type of lesion has been described previously in pellagrins[3, 8, 15, 19, 99, 131] In two of our patients, this lesion developed under observation while the patient was subsisting upon the basic diet. An analogous alteration in the



Fig 21—In addition to the typical dermatitis on the feet this patient shows a thickening and pigmentation of the skin on the knees

sebaceous glands of the rat's tail has been produced by feeding a diet similar to the basic diet used in these patients[99] There is no relation between the presence or extent of seborrhea and the severity of the disease

When the patient is confined to bed, there is a tendency toward the development of bilateral symmetrical lesions over the bony prominences of the body, such as the elbows, knees, ankles, and spinous processes These lesions are hyperkeratoses, accompanied by more or less pigmentation They differ from the dermatitis which occurs on the exposed surfaces by their slow development and by the absence of vesiculation They rarely show crust formation, induration, or secondary infection, and

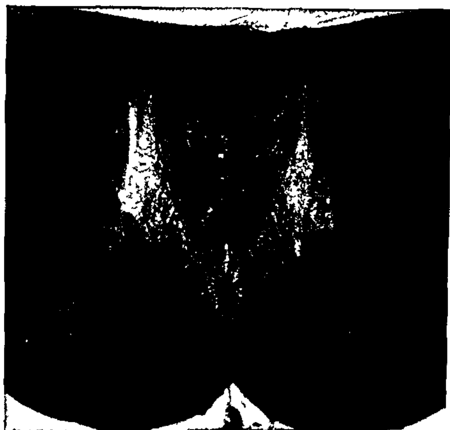


Fig 22—Lesions about the genitalia in a colored woman with typical dermatitis on the hands

their development is not accompanied by an increase in constitutional symptoms *Bilateral, symmetrical cutaneous lesions* of this type have been observed in both white and negro patients who were receiving an adequate diet and who showed no evidence of pellagra,[94] but such lesions are never as marked as those seen in pellagra We agree entirely with Bass[3] in attributing this type of lesion to mechanical rubbing or pressure over the bony prominences of the body

The male pellagrin may show lesions on the scrotum, perineum, or penis, although perineal lesions are more commonly seen in the female. Perineal lesions are red and macerated, with secondary infection. The vaginal mucosa becomes inflamed and pours out an irritating secretion. Bass[3] stated that the perineal

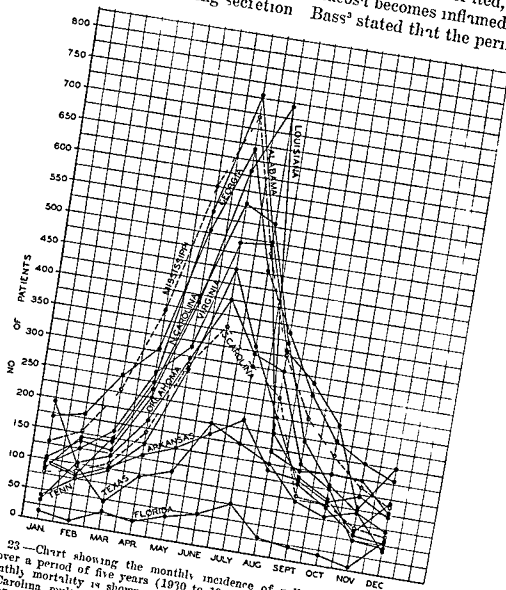


Fig 23.—Chart showing the monthly incidence of pellagra in eleven Southern states over a period of five years (1930 to 19 4). In the twelfth state (Arkansas) the monthly mortality is shown. To obtain the actual figures for Mississippi and South Carolina multiply by 10. (After Smith and Ruffin. Arch Int Med 59 631 1937.)

lesions are due to excoriating secretions and that the occasional lesions found under a pendulous breast are caused by excessive perspiration.

Seasonal Incidence of Pellagra—The seasonal incidence of pellagra (Fig 23) is apparently conditioned by two factors the degree of dietary deficiency and the intensity of the solar radiation In Fig 24 *the monthly variations in the* intensity of sunlight are shown together with the monthly incidence of pellagra As Goldberger and his associates [8] have pointed out, there is a gradually accumulating deficiency of accessory food factors during the winter months When these deficient pa

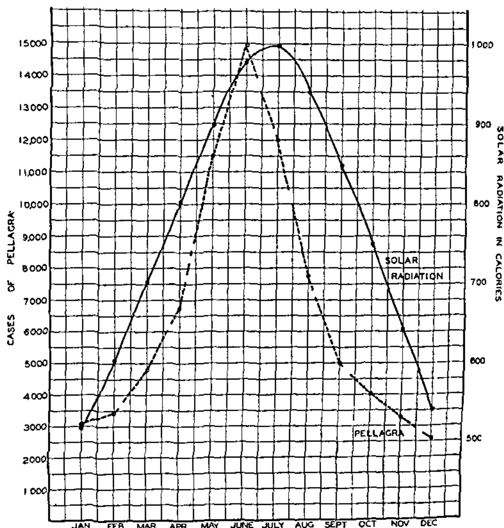


Fig 24—Chart illustrating the relationship of the intensity of the sun's rays to the incidence of pellagra One curve shows the total monthly incidence of pellagra over a period of five years in the eleven states shown in Fig 23 The curve for the total solar radiation is shown in calories per square centimeter per day on a surface at normal incidence at sea level on cloudless days for 33 degrees latitude, and was calculated for us by Prof Paul Gross, of the Department of *Chemistry of Duke University*, from the curves presented by C G Abbot in his book entitled *The Sun* D Appleton Century Company, Inc New York 1939 p 385 Fig 71 (After Smith and Ruffin Arch Int Med 59 631 1937)

tients become exposed to the increasing intensity of sunlight during the spring and early summer, the acute symptoms of pellagra appear When vegetables and milk become more plentiful during the summer, the deficiencies are corrected and the incidence of pellagra falls rapidly, although the sun remains hot during the months of July and August

Clinical Course After Exposure to Radiant Energy—The clinical course of a pellagrin after exposure to sunlight, or to heat from any source, is frequently explosive in onset and alarming in severity The usual story is that an individual subsisting upon a deficient diet, with many vague symptoms, though still able to work, exposes himself to the direct rays of the sun early in the spring or summer Within a few hours a burning and itching sensation is noted over the exposed areas, which is followed in twenty four to thirty six hours by a fiery red erythematous rash Vesiculation appears accompanied by induration, dry crusts, or secondary infection The bright red erythema changes to a dull bronze, and finally to a deep brown After the initial erythema the mouth and tongue become red and sore, and diarrhea appears Dementia may develop without warning and is always an ominous sign

Summary—Our observations support the view of Goldberger[38] that pellagra is a deficiency disease The clinical picture is one of gradually developing lassitude, anorexia mental torpor, emotional instability, vague digestive symptoms, weakness and dizziness, sometimes with, but more generally without, loss of weight The tongue frequently shows papillary atrophy, especially about the edges In some cases there is roughness of the skin, of the alae nasi, and over the forehead and face, and hyperkeratoses may appear in the region of the bony prominences Although pellagra may be suspected from these symptoms and treated as such, yet we agree with Wood[131] and Bass that it is hazardous to make a diagnosis of pellagra in the absence of typical dermatitis or a credible history of such a dermatitis on the exposed surfaces of the body

The clinical impression that exposure to sunlight is harmful to the pellagrin has been amply confirmed by observations on patients under carefully controlled conditions in Duke hospital Along with, or shortly after, the appearance of the dermatitis

one usually observed a fiery red tongue, followed by anorexia, nausea, vomiting, diarrhea, and, in some instances, dementia In several cases in this series, very severe illness has followed relatively short periods of exposure It should be emphasized, therefore, that the pellagrin should be carefully protected not only from the sun but from heat rays from any source That the exposure to sunlight was not excessive is shown by the failure of sunburn to develop in members of the staff and in students who were exposed similarly and simultaneously Furthermore, 36 of the patients who showed acute symptoms after exposure to sunshine were re exposed after the administration of an abundance of the pellagra preventive factor, and in no instance did either dermatitis or constitutional manifestations recur, showing that they had been protected by some factor or factors in the diet

The Use of Liver Extracts in the Treatment of Pellagra

Historical —The use of liver extract in the treatment of pellagra was introduced by Voegtlin[12] in 1914 While good results were reported, this form of therapy was not employed widely until many years later, probably due to the fact that liver extracts were not readily available until they were prepared commercially for the treatment of pernicious anemia

Powdered Extract —In 1930, Goldberger and Sebrell[39] showed that experimental blacktongue could be prevented and cured by a powdered extract of liver (Lilly's 343) Two years later, the beneficial effect of this extract in the treatment of human pellagra was reported by Boggs and Padget[12] It should be noted, however, that their patients were fed a well balanced diet while receiving the liver extract Since it is now generally recognized that most patients having pellagra will recover without supplemental therapy when fed a general hospital diet, an accurate evaluation of the potency of the liver extract used in their cases is impossible However, the value of this powdered liver extract has been confirmed in one patient reported by us in 1934[31] and in 2 patients studied by Fouts and his associates[31] in 1936 All of these patients were subsisting upon a deficient diet and were studied under carefully controlled conditions

Aqueous Extract of Whole Liver —In 1932, we[9] reported the successful treatment of pellagra with an aqueous extract of

whole liver (solution of liver extract—Valentine N N R) in patients who were subsisting upon a deficient diet (Table VII) A total of 22 patients have been treated with this extract in doses of 90 c c daily for seven to ten days All the patients in this series of cases either had failed to improve on the de ficient diet or else had relapsed after exposure to sunshine, and were considered therefore suitable cases for study The re sponse to this therapy was prompt and in many instances dra matic The glossitis subsided within two to four days, the ap petite returned after three to five days, the diarrhea usually ceased within seven to ten days, and the dementia frequently cleared after two to three weeks of therapy When the demen tia had existed for a month or longer, there was rarely any im provement noted Rapid and complete recovery was noted in 20 of 22 patients, and none relapsed after exposure to sunshine following the treatment (Table VIII)

TABLE VIII

BASIC DIET WITH VALENTINE S LIVER EXTRACT

(1 c c derived from 7 5 Gm)

HIST NO	BEFORE TREATMENT				TREATMENT		AFTER TREATMENT				AFTER EXPOSURE			
	DERMATITIS	GLOSSITIS	DIARRHEA	ANOREXIA	C C	DAYS	DERMATITIS	GLOSSITIS	DIARRHEA	ANOREXIA	DERMATITIS	GLOSSITIS	DIARRHEA	ANOREXIA
55083	+	+ +	0	+ + +	90	8	0	0	0	0	0	0	0	0
55963	+	+	+ + +	+	90	10	0	0	0	0	0	0	0	0
58663 (A)	+ + +	+ + +	+ +	+ + +	210	5	0	0	0	0	0	0	0	0
16778	+ + +	+ + +	+ +	+ +	90	12	0	0	0	0	–	–	–	–
20185	+ + +	+ +	0	+ + +	90	25	0	0	0	0	–	–	–	–
27215	+ +	+ + +	+	+ +	90	10	0	0	0	0	–	–	–	–
25823	+ + +	+	+	+	90	16	0	0	0	0	–	–	–	–
21054	+	+ + +	+ +	+ +	90	10	0	0	0	0	–	–	–	–
25528	+ +	+ +	0	+	90	7	0	0	0	0	0	0	0	0
66887	+	+ +	+ +	+ +	90	10	0	0	0	0	0	0	0	0
60982	+	+ +	+ + +	+ + +	90	10	0	0	+	0	0	0	0	0
68357	+ +	+	+ +	0	90	5	0	0	0	0	0	0	0	0
13113	0	+	0	+ +	90	8	0	0	0	0	–	–	–	–
40052	0	+	+	+	90	10	0	0	0	0	0	0	0	0
13011	+	+	0	+ +	90	10	0	0	0	0	0	0	0	0
14258*	+ +	+ +	+ + +	+ +	60	6	+	+	+ + +	+ +	–	–	–	–
15803	0	+ +	+	+ +	90	10	0	0	+	0	–	–	–	–
53398	0	+ +	+ +	+	90	10	0	0	0	0	–	–	–	–
26017	+ +	+	+ + +	+	90	10	+	0	0	0	–	–	–	–
4866	+ +	+ +	0	0	90	10	0	0	0	0	–	–	–	–
11803	0	+ +	+ +	+ + +	90	10	0	0	0	0	0	0	0	0
53870	+ +	+ +	+ + +	+ +	90	5	0	0	0	0	0	0	0	0

* Died A alcoholic

In this and in all subsequent tables + means a positive reaction 0 a negative one and – not tested

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25528	+ +	+ +	0	+	90	7	0	0	0	0	0	0	0	0
66887	+	+ +	+ +	+ +	90	10	0	0	0	0	0	0	0	0
50982	+	+ +	+ + +	+ + +	90	10	0	0	+	0	0	0	0	0
68337	+ +	+	+ +	0	90	5	0	0	0	0	0	0	0	0
13113	0	+	0	+ +	90	8	0	0	0	0	–	–	–	–
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14958	+ +	+ +	+ + +	+ +	60	6	+	+	+ + +	+ +	–	–	–	–
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26017*	+ +	+	+ + +	+	90	10	+	0	0	0	–	–	–	–
4866	+ +	+ +	0	0	90	10	0	0	0	0	–	–		–
11803	0	+ +	+ +	+ + +	90	10	0	0	0	0	0	0	0	0
53570	+ +	+ +	+ + +	+ +	90	5	0	0	0	0	0	0	0	0

*Died A alcoholic

In this and in all subsequent tables + means a positive reaction 0 a negative one and – not tested

Parenteral Extracts—The beneficial effect of parenteral extracts in the treatment of pellagra when the patient is subsisting upon a general diet was first reported in 1933 by Ramsdell and Magness[9] This was soon confirmed by other observers[33 46 102 104 133] Spies[102 104 108] and his associates used large doses intravenously with dramatic results, and report a reduction in mortality from 32 to 6 per cent with this method of therapy[108] However, it is important to note that his patients were fed a well balanced diet, and therefore the recovery of these patients cannot be attributed entirely to the liver extract

In our studies with the patient subsisting upon a deficient diet, the parenteral extracts were found to be only partially effective in inducing a remission[8] The acute glossitis subsided promptly in 18 of 23 patients It was noted that failure of the tongue to improve occurred in those patients receiving the extract derived from less than 400 Gm of liver There was little if any improvement in the appetite, even after enormous doses of liver extract, a result which is in sharp contrast to the effect of liver extracts in the treatment of pernicious anemia and sprue No constant effect upon the diarrhea was observed, but it was our impression that the larger doses of liver extract, given parenterally, usually resulted in improvement

Multiple Deficiency Theory—The failure of the parenteral liver extracts to effect the complete recovery, which had been observed after the use of the aqueous extract (solution liver extract—Valentine N N R), suggested (1) that the liver extract to be effective, must be given orally, or (2) that in the process of preparation some factor present in the aqueous extract was either discarded or destroyed[81 8]

To test the first hypothesis, a patient was given 140 c c daily of Lilly's intramuscular extract orally for six days This amount represented a daily dose of extract derived from 700 Gm of liver, a total dosage of 4,200 Gm This proved totally ineffective in curing the disease It seemed probable, therefore, that the missing factor had been discarded in the process of preparing the parenteral extract The addition of 95 per cent alcohol to an aqueous extract of liver results in a clear supernatant fluid, containing most of the pernicious anemia factor, and a dark brown viscid residue This supernatant fluid forms

the basis of all parenteral extracts Samples of the residue were furnished us by two manufacturers,* and these were used in the treatment of 13 patients Six patients received the Valentines residue in doses of 90 c c daily, an amount derived from 680 Gm of liver Four patients recovered completely and 2 were unimproved The remaining 7 patients received varying doses of the Lederle residue Three recovered 1 improved, and 3 were unimproved It was noted that those who recovered had received the residue derived from very large amounts of liver (19,000 to 28,000 Gm) With one exception, those who received the material derived from less than 10,000 Gm of liver failed to improve or relapsed after exposure to sunshine This residue (Lederle's) in daily doses of 90 c c (derived from 2,880 Gm of liver) promptly restored the blood to normal levels in one case of pernicious anemia and in one case of sprue This would indicate that, in large doses, the residue contains both the pernicious anemia and pellagra factors

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lagra The first experiments showed that the standard basic diet No 1 (Table VII) *would produce blacktongue in thirty to forty days when fed to dogs*[81] When we began our studies, there was some confusion in the literature on *experimental* blacktongue, since Chittenden and Underhill[17] produced this condition by feeding a diet deficient in cod liver oil but containing yeast and red meat, while Goldberger and Wheeler[43] produced blacktongue on a diet which had an abundance of cod liver oil but contained no yeast or red meat Smith, Persons, and Harvey[93] repeated both sets of experiments and found that the Goldberger type of blacktongue was the true analogue of pellagra

The various types of liver extracts used on patients with pellagra were assayed on dogs with experimental blacktongue by Harvey, *Smith, Persons, and Burns*[0] *Their results in dogs* corresponded to those obtained in patients The simple aqueous extracts of the Valentine type were very effective in curing experimental blacktongue, the parenteral extracts were only partially effective The results were apparently quantitative, and doses established on a per kilogram basis could be transferred from dog to man This quantitative study of liver fractions gave a background for a rapid assay of nicotinic acid, with the establishment of an accurate dosage, before we applied it to the treatment of pellagra[95]

Summary—When any of the parenteral liver extracts are used in conjunction with a *well balanced diet, prompt recovery usually takes place, but if the diet is deficient in the pellagra preventive factor,* these preparations are only partially effective Extracts of whole liver, however, are curative even when the patient or dog is subsisting upon a deficient diet These observations suggested that two or more factors which are necessary for the cure of the disease are present in liver

The Use of Nicotinic Acid in the Treatment of Pellagra

Historical—Nicotinic acid has been known *to chemists for* many years, and is prepared commercially by the oxidation of nicotine *It is interesting to note* that Funk[36] isolated nicotinic acid from sources rich in the vitamin B complex in 1911, but discarded it because he recognized that it was not the anti beriberi

vitamin which he was seeking. The significance of this finding was overlooked completely until interest in nicotinic acid was revived by the demonstration that it formed a part of a co-enzyme necessary for life.[8, 13] Shortly afterwards, Knight[8] discovered that meat extract could be replaced by thiamin chloride (B_1) and nicotinic acid in the cultivation of staphylococci.

Approaching the problem from a different viewpoint, Mueller[73] observed that liver extract stimulated the growth of diphtheria bacilli. He isolated nicotinic acid from a parenteral fraction of liver and found it just as effective as the liver extract in stimulating the growth of this organism.

ORIGINAL STUDIES IN ANIMALS.—Working independently, Elvehjem and his associates[5, 26] fed nicotinic acid to dogs with experimental blacktongue and produced a dramatic recovery. They then isolated nicotinic acid amide from a fraction of liver known to be effective in the treatment of blacktongue. This epoch-making discovery of Elvehjem was soon confirmed by other investigators.[21, 26, 68, 90, 98, 113] Dann and Subbarow found that nicotinic acid was ineffective in the treatment of so-called "rat dermatitis" and "chick dermatitis" which at one time were considered analogues of human pellagra.

ORIGINAL STUDIES IN HUMAN PELLAGRA.—The beneficial effects of nicotinic acid in the treatment of human pellagra were demonstrated independently and simultaneously by four different groups of workers. The first published report showing the potency of this material was by Fouts and his associates[30] in November, 1937. On December 18, 1937, there appeared two communications, one by Harris[48] and the other by Smith, Ruffin and Smith,[9] reporting the effectiveness of nicotinic acid in pellagra. Spies, Cooper, and Blankenhorn[109] reported a series of 17 cases in February, 1938. Since then there have been numerous reports of the successful use of nicotinic acid in the treatment of pellagra.[11, 34, 5, 66, 78, 105, 106, 107, 115]

It is of interest to note that doses of 500 to 1,000 mg. per day were employed by Fouts and his associates, by Harris, and by Spies, Cooper, and Blankenhorn. In contrast to these large doses, the patient reported by us recovered promptly after the administration of only 70 mg. per day. The efficacy of this

small dose has been confirmed by subsequent studies at Duke Hospital[83] and by France, Bates, Barker, and Matthews[34] of the Johns Hopkins Hospital

Experimental Studies in Animals—Harvey, Smith, Persons, and Burns[50] devised a method for assaying the blacktongue curative dose of liver extracts The curative dose for the dog, calculated on the basis of kilograms of weight, was proved to be applicable to the treatment of patients with pellagra When Elvehjem and his associates[5] reported that nicotinic acid cures experimental blacktongue, it seemed advisable to determine by this standardized method the optimal and minimal curative doses for the dog before attempting to treat patients with this new drug Margolis, Margolis, and Smith[68] treated 26 dogs in 35 attacks of acute experimental blacktongue with nicotinic acid and compared the results with those obtained in 18 dogs treated with the most effective liver fractions The daily dose employed in the dog varied from 0 1 mg to 10 mg per kilogram of body weight The 0 1 mg dose failed to cure and the 0 2 mg dose was only slowly effective Doses of 0 5 mg resulted in rapid and dramatic cure, and doses twenty times as large (10 mg) were no more effective (Fig 25) In one series of experiments, the nicotinic acid was dissolved in physiologic saline (0 85 per cent) in a concentration of 5 mg per c c, and after sterilization by boiling or autoclaving, was given intramuscularly to one group of dogs and orally to another At a level of 1 5 mg per kilogram the oral treatment was as effective as the parenteral Intravenous treatment in dogs was harmless and effective but failed to induce the red reaction in the skin which was later found to be a constant phenomenon when nicotinic acid was given intravenously to patients

Excretion of Nicotinic Acid in the Urine—Nicotinic acid when fed to dogs is excreted in the urine as (1) free nicotinic acid, (2) trigonelline, and (3) nicotinuric acid[1, 61] Attempts have been made by Vilter, Spies, and Mathews[11] to measure the excretion of nicotinic acid in the urine The figures on nicotinic acid excretion in normal individuals, published by these authors, could not be confirmed in the Biochemical Laboratory at Duke University on attempting to apply the analytical technique described by them A method based upon the well known reaction

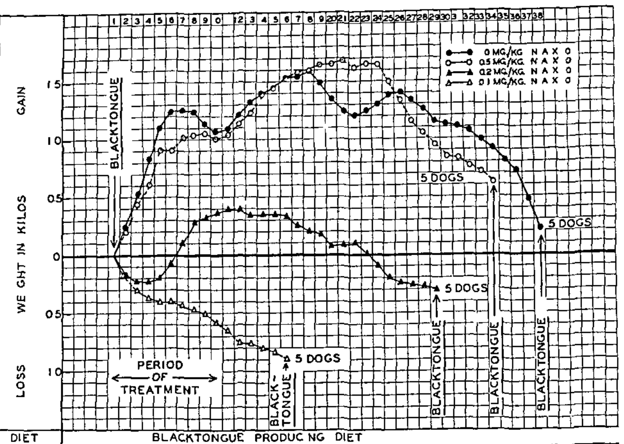


Fig 25.—Comparison of growth response of blacktongue dogs treated with different dosage levels of nicotinic acid as follows 0 1 mg 0 2 mg 0 5 mg and 10 0 mg per kilogram of body weight daily for ten days (After Margolis George Margolis Lester H and Smith Susan Gower J Nutrition 16 541 1938)

of pyridine derivatives with cyanogen bromide and anilin has been worked out by Perlzweig and Levy[77] and is being employed now for the study of the excretion of nicotinic acid and its derivatives under normal and experimental conditions. Fraser[35] has measured the excretion of nicotinic acid and related substances in dogs' urine by testing for their growth stimulating properties on dysentery bacilli. They found that the growth factor decreased as the dogs developed blacktongue and was restored to normal after treatment with nicotinic acid. McCrea[64] noted that nicotinic acid in doses of 1 to 2 mg. per kilogram intravenously produced a transient but definite increase in blood pressure in cats and dogs.

Toxicity in Animals.—Chen and his associates[16] found that continuous treatment with 2 Gm. of nicotinic acid daily produced death in two dogs. Unna Klaus,[5] however, observed that dogs were unaffected by the administration of sodium nicotinate in doses of 1 Gm. per kilogram given daily for several months.

The Relationship of Nicotinic Acid to Coenzymes.—Very little is known about the action of nicotinic acid and related compounds in the body. Warburg's[1,3] and von Euler's[8] coenzymes are similar to, if not identical with, the V factor needed for growth of *H. parainfluenzae*. Kohn[60] studied the concentration of coenzyme-like substances in his own blood while subsisting on a modification of Ruffin and Smith's standard basic diet for a period of forty days. The coenzyme-like substances never went below the normal level but could be increased by 50 per cent within two days by taking 20 mg. per kilogram of weight within a twenty-four hour period. Some of the pellagrins studied by Kohn showed a decrease in the level of the coenzyme-like substance, and all of them responded with a rapid increase in this substance when given nicotinic acid. The rapidity of the rise was roughly parallel to the size of the dose.

Effect of Nicotinic Acid Upon Normal Individuals.—In an effort to determine the effect of large doses of nicotinic acid in normal individuals, 13 medical students, who volunteered, were selected for experimental study. Ten were given 1 Gm. of nicotinic acid per day in capsules, divided into four doses, and 3 were given lactose in similar capsules, so that the student was unaware of what he was receiving. The three controls experi-

enced no reactions whatever Each of the students taking nicotinic acid complained of flushing of the face and neck However much more serious symptoms were noted marked mental depression epigastric distress, substernal oppression, headache, nausea, and vomiting (Table IX) Although the experiment was planned for ten days, 5 of the students felt so badly that they stopped taking the capsules after the second day

TABLE IX

SYMPTOMATOLOGY OF 10 MEDICAL STUDENTS AFTER INGESTION OF 1 GM OF NICOTINIC ACID DAILY (250 MG 4 TIMES A DAY)

Flushing of face and neck	10
Lassitude and mental depression	5
Burning in epigastrium	4
Palpitation	3
Cyanosis of nails	2
Substernal oppression	2
Headache	2
Nausea	2
Dyspnea	1
Vomiting	1

Five of the ten students felt so badly that they discontinued the experiment after the second day

In contrast to these observations, Bean[5] reports that little or no ill effects were noted after the use of large doses in normal individuals He states "We have given a single oral dose of 1 5 Gm , we have given 1 7 Gm daily for 10 days and we have given 1 Gm daily for six weeks to normal adults without any evidence of depression, cyanosis, or marked gastro intestinal disturbance, and no other event besides the flushing rise in skin temperature, and occasional epigastric distress which we have shown to be associated with increased peristalsis " However, Sydenstricker and his associates[11] found that 0 25 to 1 Gm doses in normal controls produced definite toxic symptoms similar to those reported by us They state "Doses of 250 to 1,000 mg caused increased flushing with painful paresthesias, salivation slight tachycardia and in two instances dyspnea and substernal oppression "

The observations made at Duke Hospital, and those of Sydenstricker, would indicate that nicotinic acid is definitely toxic and the indiscriminate use of large doses is to be avoided

Dosage in Patients—After it had been determined that the dog curative dose was 0 5 mg per kilogram of body weight, it

was decided to use three times this dose or 1 5 mg per kilogram daily in the treatment of human pellagra In the patients studied, this amounted to 100 mg or less per day This dose was found to be highly effective in critically ill patients when administered in solution either orally, intramuscularly, or intravenously The drug is not readily soluble, and, when given in tablets or in capsules, less satisfactory results were obtained When used orally the dose should be larger, 100 mg two or three times daily, because of its relative insolubility



Fig 26—*Dermatitis on dorsum of hands in Case 09183* (Table XI) (After Ruffin and Smith South M J 32 40 1939)

Preparations of Nicotinic Acid—Nicotinic acid is available commercially in crystalline form, in tablets, and in capsules It is poorly soluble in water and in physiologic saline, and, in general, one can dissolve only 5 mg per c c This solution can be sterilized by boiling or by autoclaving[98] *without loss of* potency and can be kept for weeks without deterioration The solution made from the crystals is probably the most economi

cal preparation for hospital use For oral administration, the drug should be dissolved in water The parenteral preparation, however, should be made with normal saline

Methods of Administration—For critically ill patients, the intravenous administration of nicotinic acid is highly desirable The solution should be added to 500 c c of 5 per cent glucose in normal saline and administered slowly This is almost invariably accompanied by a marked flushing of the face and neck, and frequently of the entire body, which fades after fifteen to twenty minutes The patient experiences, as a rule, a subjective sensation of warmth and tingling of the skin, and occasionally an urticaria appears which soon subsides The glucose



Fig 27—Same patient as shown in Fig 26 after treatment with nicotinic acid (After Ruffin and Smith South M J 32 40 1939)

and saline should be used not only as a vehicle for the nicotinic acid but also to combat the dehydration and acidosis which usually are present in severe cases

Unfavorable reactions are rare when the drug is given orally in doses of 100 mg It is more desirable to give 100 mg three to four times a day rather than a single large dose Doses of 250 mg have been found to cause very unpleasant symptoms in normal individuals It also has been noted that the drug is

tolerated better when given after meals The fact that flushing occurs after the ingestion of the drug does not indicate necessarily that an adequate amount has been absorbed, because 10 to 15 mg given intravenously will produce similar flushing

Pellagrins Treated With Nicotinic Acid —From Nov 1, 1937 to Nov 1, 1938, 85 patients with pellagra have been studied at Duke Hospital All patients in this group had the characteristic dermatitis and one or more constitutional symptoms However, 40 of these were considered to be either mild or subsiding

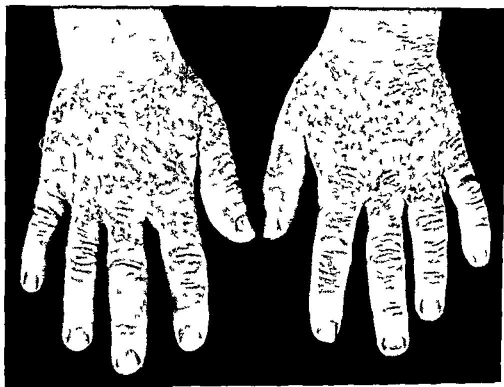


Fig 28 —Dermatitis on dorsum of hands in Case 98075 (Table XI) (After Ruffin and Smith South M J 32 40, 1939)

cases and were not included in this study The remaining 45 patients were hospitalized Eighteen of these patients had complicating diseases rendering them unsuitable for experimental study, and therefore were fed an amplified diet Seven of this group were given nicotinic acid, 30 to 80 mg daily, and recovered Eleven were treated with various extracts of liver One patient in this group was moribund and died twelve hours after admission Another died of generalized peritonitis The other 9 patients recovered

The remaining 27 patients were fed a basic diet, deficient in the B complex (Table X) The necessity of demonstrating that the patient had active pellagra before attempting the evaluation of any curative material has been emphasized in previous publications[81,83] In this group, 10 patients improved on the basic diet or failed to relapse after exposure to sunshine They were then fed an amplified diet supplemented by nicotinic acid and all made a satisfactory recovery The remaining 17 patients

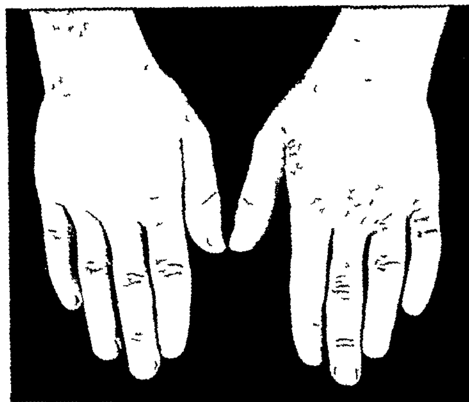


Fig 29—Same patient as shown in Fig 28 after treatment with nicotinic acid (After Ruffin and Smith South M J 32 40 1939)

were considered as active pellagrins and suitable cases for study It should be emphasized that *of 95 patients suffering from clinical pellagra only 17 were found suitable for the critical evaluation of the therapeutic efficacy of nicotinic acid* The results of treatment in these 17 cases are shown in Table XI (Figs 26 27, 28, and 29)

Effect of Treatment—The response to treatment with nicotinic acid usually is *prompt* and in *many* instances dramatic Desperately ill patients, who undoubtedly would have died be

TABLE X

STANDARD BASIC DIET No 3

ARTICLE	QUANTITY (GM)	PROTEIN (GM)	FAT (GM)	CARBOHYDRATE (GM)	MINERALS			VITAMINS					CALORIES
					CALCIUM	PHOSPHORUS	IRON	A	B	C	D	G	
Corn meal	92	8 3	2 0	69 0	0 0110	0 1225	0 0006	--	+	--	--	±	
Cane syrup	105			89 2				--	+	--	--	+	
Flour	111	12 5	1 2	83 4	0 0220	0 1030	0 0010	--	+	--	--	-	
Lard	81		81 0					--	-	--	--	-	
Rice	25	2 0	0 1	19 6	0 0023	0 0240	0 0002	--	-	--	--	-	
Field peas	90	19 2	1 4	54 6	0 0756	0 0760	0 0052	+	++	--	--	+	
Hominy grits	51	4 3	0 3	0 3	0 0056	0 0734	0 0005	--	+	--	--	-	
Fat salt pork	60	1 1	51 3	51 3	0 0011	0 0115	0 0001	--	-	--	--	-	2890 0
Cheese	60	17 4	21 6		0 5586	0 4098	0 0007	++	++	--	--	+	264 0
Total		64 8	158 9	367 4	0 6762	0 8202	0 0093						3154 0

TABLE XI

BASIC DIET PLUS NICOTINIC ACID (17 PATIENTS)

HISTORY NO	AGE	RACE	SEX	DERMATITIS BEFORE	DERMATITIS AFTER	GLOSSITIS BEFORE	GLOSSITIS AFTER	ANOREXIA BEFORE	ANOREXIA AFTER	DEMENTIA BEFORE	DEMENTIA AFTER	DIARRHEA BEFORE	DIARRHEA AFTER	MG N A PER DAY	COMMENT
81690	50	W	F	++	0	++	0	+	0	0	0	0	0	100	Prompt recovery
A-1970	8	W	M	++	0	+	0	+++	0	+	0	+	+	30	Recovery
A-2[illegible]5	40	W	F	++	0	+	0	+	0	0	0	0	0	100	Recovery
56821	42	W	M	++	0	++	0	+	0	0	0	0	0	90	Recovery
A-1814	24	C	M	+++	0	+++	0	+++	0	+++	0	++	0	100	Very ill recovery
A-4749	64	W	M	+++	0	+	0	++	0	0	0	0	0	100	Recovery
A-4629	63	W	F	++	0	+++	0	+++	0	0	0	+	0	60	Recovery
9[illegible]075	54	W	M	+++	0	+++	0	+++	0	0	0	+++	0	90	Very ill, recovery
A-47[illegible]5	42	W	F	+++	0	+++	0	+++	0	0	0	+	0	90	Recovery, myxedema also
99183	65	W	M	+++	0	+++	0	+++	0	+++	0	+++	0	90	Very ill recovery
82333	52	W	F	+	0	++	0	++	0	+	0	0	0	60	Recovery
92749*	42	W	M	+++	0	+	0	+++	0	+++	0	0	0	60	Recovery
A-9275	40	W	M	+	0	+	0	+++	0	+++	0	0	0	82	Recovery
68486	52	W	M	+++	0	++	0	+++	0	0	0	0	0	1000	Recovery
A-2834	36	W	M	+	+	+	+	+++	+++	+++	+++	++	+++	100	Died†
A-3111	25	W	F	++	0	++	0	0	0	0	0	0	0	3 cc ‡	Recovery
A-3268	30	C	F	++	0	+++	0	+++	0	0	0	0	0	3 cc ‡	Abscess of buttocks recovery

* Previously reported

† Alcoholic with Korsakoff's syndrome No improvement after four days treatment with thiamin chloride (100 mg./day)

‡ Coramine

fore the discovery of the value of the drug, have been restored to health by its use It should be pointed out, however, that in pellagra, as in other vitamin deficiencies, if the disease has progressed beyond a certain critical point, therapy is of no avail and the patient succumbs in spite of treatment

GLOSSITIS —The first noticeable effect of the treatment is on the glossitis Within twenty four hours the fiery redness of the tongue disappears, and ulcers beneath the tongue and on the lips usually heal after three to five days (Table XII) Accompanying these changes, the patient experiences a marked and most gratifying relief The papillae will regenerate within seven to fourteen days

ANOREXIA —The anorexia which is a very constant symptom in active pellagra disappears after a few days of treatment except in an occasional patient in whom other deficiencies, especially B_1, co exist In these cases the appetite may not return until the nicotinic acid has been supplemented by thiamin chloride Occasionally the anorexia reappears while the patient is being treated with nicotinic acid The administration of thiamin chloride at this point usually will result in marked improvement

NAUSEA AND VOMITING —Nausea and vomiting are not seen frequently and occur only in the acutely ill patients These symptoms usually subside promptly after the administration of nicotinic acid, along with the general improvement in the patient

DIARRHEA —Diarrhea is by no means a constant symptom in mild or moderately severe pellagrins (Table XII) It is generally present in very ill patients, and its development should be regarded as an ominous sign It subsides as a rule five to ten days after the administration of nicotinic acid

PSYCHOSES —Mental symptoms are extremely common, varying from nervousness and irritability to actual psychoses with delusions and hallucinations With the exception of its effect upon the glossitis, the change in the patient's mental condition following the use of nicotinic acid is the most spectacular and dramatic result of the treatment Within four to five days after its administration, patients who had been completely disoriented and irrational become entirely normal In our experience with

TABLE XII

EFFECTS OF NICOTINIC ACID, "CORAMINE," AND LIVER EXTRACTS UPON SYMPTOMS OF PELLAGRA

	TOTAL CASES	DERMATITIS		SEB GLANDS		PERINEAL LESIONS		ANOREXIA		GLOSSITIS		DEMENTIA		DIARRHEA	
		CASES	DAYS*	CASES	DAYS	CASES	DAYS	CASES	DAYS	CASES	DAYS	CASES	DAYS	CASES	DAYS
Nicotinic acid	15	13	11	7	12	1	5	13	4	12	3	4	10	4	8
"Coramine"	2	2	10	1	10	1	13	1	3	2	3				
Aqueous Ext of whole liver	31	24	7	3	7	9	9	25	5	27	4	10†	10	18	7‡

*Average number days before subsidence of symptoms
†Three still demented at time of discharge
‡One had diarrhea at time of discharge

nicotinic acid, the psychoses have responded to treatment (Table XII), but it would be hazardous to predict that psychoses which have been present for months will improve in a similar manner The first published report showing the beneficial effect of nicotinic acid in the treatment of the psychoses of pellagra was by Smith, Ruffin, and Smith in December, 1937[95] Since then this observation has been confirmed by various observers[11 70 78 106] The most extensive studies of the effect of nicotinic acid on the psychoses of pellagra are by Matthews[0] and Spies and his associates[106]

In a report by Jolliffe, Bowman, Rosenblum, and Fein (J A M A 114 1940), 150 patients having what is called an "encephalopathic syndrome" are discussed This syndrome is characterized by "clouding of consciousness, cogwheel rigidity of the extremities, and uncontrollable grasping and sucking reflexes," and occurs usually in chronic alcoholics with or without pellagra Treatment by parenteral fluids alone or with thiamin chloride did not prevent the death of 60 out of 62 consecutive patients In contrast to this the administration of nicotinic acid in doses of 100 to 200 mg by mouth every hour for 5 doses resulted in recovery of 15 out of 22 patients The authors consider this syndrome a manifestation of a total nicotinic acid deficiency

DERMATITIS —It has been pointed out earlier in this discussion that there are four types of dermatitis seen in pellagra (1) the rash over the exposed surfaces, (2) the thickening and pigmentation over the bony prominences, (3) perineal and genital lesions, and (4) sebaceous gland changes over the face

The rash over the exposed surfaces tends to fade when protected from the rays of the sun However, when secondary infection is present the rash will persist for weeks or months unless some curative substance is given Following the administration of aqueous extracts of whole liver, the rash usually improves within a few days, but it may require seven to fourteen days before disappearing completely It is of the greatest interest to note that no matter how severe the lesions may appear, healing is always complete and scars are rarely if ever seen The dermatitis heals after treatment with nicotinic acid

but usually somewhat more slowly than when aqueous extracts of whole liver are employed (Table XII)

The lesions over the bony prominences subside after seven to ten days, and the genital lesions require about the same length of time

The seborrhea over the face clears up after four to seven days of treatment with the liver extracts and will also respond to treatment with nicotinic acid, although it is our impression that these lesions persist longer under nicotinic acid treatment (Table XII)

The Use of Related Pyridine Compounds in Blacktongue and Pellagra

Woolley, Strong, Madden and Elvehjem[13] found nicotinic acid amide, diethyl amide of nicotinic acid ("coramine"), and beta picoline effective in the treatment of experimental blacktongue Picolinic acid, isonicotinic acid, nipecotic acid, quinolinic acid, 6 methyl nicotinic acid, trigonelline, pyridine, and 1 methyl nicotinic acid amide chloride were not effective in curing blacktongue

Spies, Grant, and Huff[111] have tried a number of these new compounds on patients with pellagra Alpha picoline, beta picoline, trigonelline, and beta aminopyridine had no curative effect Dinicotinic acid, 2 6 dimethyl pyridine 3 5 carboxylic acid, nicotinic acid amide, sodium nicotinate, and diethyl amide of nicotinic acid ("coramine") were effective in pellagra Minimal curative doses have not been determined for any of these compounds in dogs with blacktongue, or patients with pellagra With the exception of "coramine," there is not sufficient experimental data available to justify their use on patients with pellagra

Diethyl Amide of Nicotinic Acid ("Coramine") —Spies and his associates[107] reported excellent results in 11 pellagrins who received 4 to 20 c c of coramine daily Later[106] 8 pellagrins with dementia were treated with 2 to 5 c c daily by oral administration until the patient had received 50 c c of the drug Spies reports results comparable to those obtained with nicotinic acid Sydenstricker and his associates[115] have not obtained favorable responses with coramine They report 2 cases

of pellagra in patients who failed to improve after receiving orally 24 c c of coramine daily A third patient improved rapidly after receiving 4 c c t i d, parenterally for five days, but relapsed in two days when the drug was withdrawn Ruffin and Smith[8] reported excellent results in 2 patients who received 3 c c of coramine intramuscularly for four days and 1 c c daily thereafter These conflicting results might be explained if there were severe secondary deficiencies in the diets of the pellagrins treated by Sydenstricker[115]

A series of experiments with coramine in blacktongue dogs has been carried out in this hospital Daily doses of coramine having the molecular equivalent of 10 mg of nicotinic acid per kilogram of body weight were found to be quite as effective as the standard dose of nicotinic acid Doses of 2 mg per kilogram had variable effects, sometimes resulting in dramatic cure and sometimes in complete failure This suggests that the *coramine is broken down in the animal's body to nicotinic acid* and that this rate of breakdown may vary in different dogs Coramine is more expensive than nicotinic acid but has the advantage of being more soluble, can be administered more conveniently intramuscularly, and does not produce the violent flushing symptoms noted with nicotinic acid

Secondary Deficiencies in Pellagra

B_1 Deficiency—Peripheral neuritis is present in most patients with "alcoholic" pellagra[10] By substituting alcohol for food the patient becomes deficient in both the pellagra preventive factor and B_1 The work of *Minot, Strauss, and Cobb,*[7] *of Spies and DeWolf,*[110] of Strauss,[112] and of Blankenhorn and Spies[10] shows that peripheral neuritis is not produced by alcohol if the diet contains an adequate amount of thiamin chloride

Our experience in North Carolina[83] and Sydenstricker's[116] work in Georgia indicate that peripheral neuritis is not very common in endemic nonalcoholic pellagrins It is most frequent in chronic cases where the anorexia of pellagra results in an inadequate consumption of food These clinical observations are supplemented by the experimental work of Margolis, Margolis, and Smith,[69] who found that dogs subjected to repeated attacks of experimental blacktongue developed a secondary de

1



2





3



4

PLATE II

1—*Colored photograph taken on admission July 11 1939 showing the face and tongue of a patient having acute pellagra*

2—Appearance of the patient on July 17 1939 The patient had subsisted upon a deficient diet and had received 50 mg of riboflavin intravenously daily for five days No appreciable change was noted

3—Appearance of the face and tongue after two days of treatment with 3 cc of coramine intramuscularly daily As will be seen the tongue had cleared up almost entirely and the lesions of the face were markedly improved

4—Appearance of patient after nine days of treatment with coramine Now entirely well He had subsisted upon a deficient diet throughout the whole period of treatment

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The same spectacular results are observed in the treatment of acute pellagra when nicotinic acid or nicotinic acid amide in d[illegible] of 100 mg daily is u[illegible]

ficiency of B_1 although the basal diet, by calculation, contained an adequate amount of B_1. Control animals, eating the same diet but protected from blacktongue by continuous treatment *with nicotinic acid, failed to develop either blacktongue or evi*dence of B_1 deficiency.

Before the introduction of thiamin chloride, Ruffin and Smith[8] found that purified B_1 from rice polishings failed to cure pellagra. The pellagrous anorexia persisted and the pa*tients were still susceptible to the deleterious effect of sunlight*.

Spies and Aring[103] noted that treatment with thiamin chloride (B_1) improved the peripheral neuritis but had no effect on the classical symptoms of pellagra. Ruffin and Smith[83] studied two alcoholic pellagrins with peripheral neuritis while the patients were subsisting on standard basic diet No. 3 (Table X). The administration of thiamin chloride in doses of 100 mg. *per day* resulted in improvement in the neuritis, although the symptoms of pellagra remained unchanged or became accentuated. The administration of nicotinic acid to pellagrins with peripheral neuritis results in rapid improvement in the pellagra but has no effect on the peripheral neuritis.[83, 10] When peripheral neuritis is present, thiamin chloride in doses of 20 to 40 mg. per day should be given along with nicotinic acid.

Riboflavin Deficiency in Experimental Blacktongue and in Pellagra.—In 1933 Sebrell[8] reported the occurrence of a new deficiency syndrome in dogs characterized by sudden collapse and death. At necropsy the liver was found to have a peculiar yellow color and was filled with fat. Later work by Sebrell and his associates,[89] Zimmerman, Cowgill and Fox[134] showed that this deficiency could be prevented or cured with pure riboflavin. However, Koehn and Elvehjem[9] failed to prevent the development of experimental blacktongue with a flavin supplement, and Sebrell, Onstott, and Hunt[91] were unable to cure blacktongue with relatively large doses of synthetic riboflavin. Three groups of clinicians, working independently, demonstrated that riboflavin would not cure pellagra.[9, 1, 82]

Although riboflavin deficiency is not the cause of pellagra, it may occur as an associated or secondary deficiency. Sebrell and Butler[88] recently reported the development of riboflavin deficiency in 10 out of 18 women who were eating a modification

of the diet used by Goldberger and Tanner[40] Small sores, resembling perleche, appeared at the corners of the mouth, there was denudation of the mucosa along the line of closure on the lips, and a fine, scaly, slightly greasy desquamation on a mildly erythematous base in the labial folds, on the alae nasi, in the vestibule of the nose, and on the ears The lesions were not improved by treatment with nicotinic acid but responded readily to daily doses of 1 or 5 mg of riboflavin The symptoms of this disease, which Sebrell calls "ariboflavinosis," were identical with those produced experimentally by Goldberger and Tanner[40] in 1925 and by Wheeler[129] in 1933

In a later communication by Kruse, Sydenstricker, Sebrell, and Cleckley (Public Health Reports, 55 No 4, 1940), it is stated that the manifestations of riboflavin deficiency in man are cheilosis, seborrheic accumulation of the nasolabial folds, a specific type of glossitis characterized by flattened papillae with a purplish red color of the tongue, and ocular lesions, especially keratitis All these lesions subsided after the daily administration of 5 mg of riboflavin by mouth

In many patients having clinical pellagra we have observed the cheilosis and seborrheic changes but have not recognized the purplish colored tongue with the flattened papillae nor the keratitis We have also noted the development of cheilosis and seborrheic lesions in two pellagrins during the control period of observation while they were subsisting on the standard basic diet No 3 (Table X) These lesions in our patients disappeared *completely with nicotinic acid therapy, although much more* slowly than we anticipated from the results of our previous experience with similar cases treated with yeast or whole liver The apparent conflict between our results and those of Sebrell is very probably explained by differences in the basic diets Our diet contained 5 times as much peas, and in addition 60 Gm of cheese, both of which foods contain appreciable amounts of riboflavin The condition probably developed because our patients had the typical anorexia of pellagra, and failed to eat the foods containing riboflavin until the appetite was restored by the nicotinic acid therapy

In the spring of 1939 two patients having typical pellagra, marked seborrheic changes over the nose, and cheilosis were

fed the basic diet and treated with 50 mg of riboflavin intravenously daily for five days The first patient showed slight improvement in the seborrheic lesions after twenty four hours, but these remained stationary during the next four days The second patient was unaffected by the administration of riboflavin Both patients promptly recovered with other treatment The first received 100 mg of nicotinic acid intravenously and the second 3 c c of coramine intramuscularly daily for a period of ten days

The fact that the seborrheic lesions heal more rapidly after the administration of whole liver extract and autoclaved yeast than after treatment with nicotinic acid, riboflavin, or both, suggests that these lesions are due to several deficiencies, two of which are riboflavin and nicotinic acid

It is fortunate that man develops ariboflavinosis in a mild, chronic form, which Sebrell was able to study for forty to forty five days before instituting therapy, rather than the acute, rapidly fatal analogue found in the dog

Summary—Pellagrous patients usually present multiple deficiencies The chief symptoms are caused by the primary defect in the diet, although certain of the associated symptoms may be due to the secondary deficiencies However, pellagrins generally make a complete recovery when the primary defect in the diet is corrected This results in marked improvement in the appetite and probably in absorption and utilization of food In the studies recently reported by Ruffin and Smith,[83] the patients were fed the standard basic diet No 3 (Table X) without the supplement This diet is known to be deficient in calcium, iron, vitamins A, C, D, and the pellagra preventive factor, but contains a moderate amount of B_1 Most of the patients made a dramatic recovery when treated with nicotinic acid alone, and only a few required the addition of B_1

These results are in sharp contrast to the previously reported studies with fractions of liver where the data suggested that there were two or more factors in liver necessary for optimal results in the treatment of experimental blacktongue[50] and pellagra[8] In these studies it was found that crude aqueous extracts were entirely satisfactory, but the parenteral preparations were only partially effective The parenteral prepara

tions of liver failed to restore the appetite or to heal the seborrhea and did not protect the patient from the toxic effect of sunlight The first reports on the use of nicotinic acid showed that dogs with experimental blacktongue[1, 26, 68, 113] and patients with pellagra[11, 34, 5, 106, 107] are uniformly cured with nicotinic acid alone More extensive experiments in animals and additional observations of patients indicate that secondary deficiencies may occur which, if not corrected, will interfere with the therapeutic response to nicotinic acid Sebrell and his associates[90] found that the continuous administration of nicotinic acid to dogs, subsisting upon a blacktongue producing diet, protected them from blacktongue, but allowed the development of a fatal *riboflavin deficiency*

Margolis, Margolis, and Smith[69] have confirmed Sebrell's discovery that riboflavin becomes a secondary deficiency and have found in addition a secondary B_1 deficiency which appears when the dogs are subjected to repeated consecutive attacks of blacktongue and treated with nicotinic acid Under the conditions of these experiments the blacktongue was cured, but the animals failed to eat properly and to gain weight (Fig 30) The addition of B_1 corrected the secondary deficiency and then the dogs responded in a satisfactory manner to nicotinic acid treatment Helmer and Fouts[3] fed the blacktongue producing diet to rats and found that nicotinic acid alone did not improve the condition of the animals, that purified liver extracts were only partially effective, while crude powdered extracts were entirely effective in restoring the rats to normal

These animal experiments are of significance in view of the report of Schmidt and Sydenstricker[8] who found that pellagrins living on a very restricted diet and treated as out patients showed temporary improvement with subsequent relapse when given nicotinic acid continuously Although the patients studied at Duke Hospital usually showed dramatic improvement with nicotinic acid, a longer period of treatment was required to heal the dermatitis of the extremities and the seborrhea than had been previously observed after treatment with aqueous extracts of whole liver

These observations and experiments indicate that nicotinic acid cures the cardinal symptoms of active pellagra, namely,

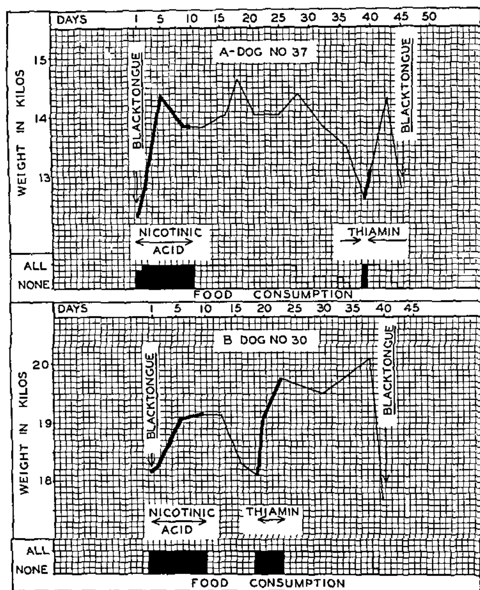


Fig 50—(*A*) Anorexia and weight loss in the absence of blacktongue after second treatment with nicotinic acid and subsequent weight and appetite response to vitamin B (thiamin) while the mouth symptoms progressed to severe blacktongue (*B*) Weight response in fourth treatment with nicotinic acid and subsequent weight gain with vitamin B (thiamin) This curve demonstrates adequate storage of nicotinic acid in vitamin B deficiency (After Margolis Lester H Margolis George and Smith Susan Gower J Nutrition 17 63 1939)

the dermatitis, glossitis, anorexia, diarrhea, and dementia. However, if other marked deficiencies co-exist, and are not corrected, they will interfere seriously with the curative effect of nicotinic acid. This new work supports our previous view that two or more factors are present in liver, all of which are necessary for the prompt cure of acute pellagra.

Treatment

The Treatment of Mild Cases.—Mild cases of pellagra, as a rule, recover promptly when fed a well balanced diet, containing red meat, eggs, fresh vegetables, milk, and fruits. When such a diet is available no other treatment is necessary, although the patient should be advised to avoid exposure to direct sunlight until all symptoms of the disease have subsided.

The Treatment of Moderately Severe Cases.—The patients having moderately severe pellagra should be confined to bed, either at home or in the hospital. In addition to a well balanced diet they should receive dried yeast, liver extracts, or nicotinic acid. The yeast should be given in doses of 1 to 2 ounces (30 to 60 Gm.) daily in water. An aqueous extract of whole liver (Valentine's liver extract) in doses of 1 tablespoonful (15 c.c.) three times a day is curative. Nicotinic acid is the cheapest form of therapy. It may be given in tablets or capsules, 100 mg. 2 or 3 times a day, or preferably 100 mg. in solution once or twice daily by mouth.

The Treatment of Severe Cases.—Severely ill patients, especially those with diarrhea and dementia, should be hospitalized invariably and treated as emergency cases. It is a common observation that patients of this type, even though they do not appear critically ill, may go into collapse and die within twenty-four hours. Probably the most important treatment in these cases is the prompt administration of glucose and saline intravenously. Continuous saline infusions may also be necessary to combat the dehydration. The diet in this stage of the disease is of little importance, as the acute glossitis, anorexia, nausea, and vomiting may prevent the ingestion of food or even of liquids. Yeast is obviously of little value. An aqueous liver extract (Valentine's liver extract), 30 c.c. (1 ounce) t.i.d., is effective if it can be retained. The best treatment for such cases

is the intravenous administration of nicotinic acid in doses of approximately 100 mg per day This is most conveniently given by adding the nicotinic acid solution to the glucose and saline This is continued until the gastrointestinal symptoms have subsided, and then the patient is given a full liquid diet After a few days a well balanced diet is given When the patient is able to eat, the intravenous treatment may be discontinued and the nicotinic acid given by mouth, 100 mg once or twice daily

In our experience it is not necessary to treat the local lesions of pellagra Mouth washes, wet dressings for the dermatitis, tincture of opium, and bismuth for the diarrhea are not only useless but may be actually harmful

Mortality

In a series of 244 patients treated in Duke Hospital, there have been 17 deaths, or 7 per cent mortality This includes 6 patients who died either of pneumonia or generalized peritonitis Since the introduction of nicotinic acid, 3 patients out of 85 have died, a mortality of 3 5 per cent One of these was moribund on admission, another died of a generalized peritonitis

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CHAPTER XVI

STUDIES ON PELLAGRA AT THE UNIVERSITY OF GEORGIA

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Introduction—The tremendous advances in fundamental knowledge regarding the various components of the "B group" of vitamins which have been made during the past five years relegate much of this chapter to purely historical interest Certain of the old problems remain unsolved and many new ones arise with changing concepts of the deficiency diseases

The discovery that nicotinic acid is curative of many of the manifestations of pellagra has opened up a new line of investigation which may alter many existing theories of nutritional deficiencies Following demonstration of the rapid efficacy of nicotinic acid in pellagra, it was obvious that its site of action must be looked for in the only substance occurring in the body of which it is known to be a component The cozymase of von Euler and the coferment of Warburg contain nicotinic acid amide and the latter contains riboflavin as well The presence of these vitamins in codehydrogenase and cocarboxylase suggests their vast importance in the combustion phenomena of cell metabolism It is possible that a lack of any of these component enzymes may result in phenomena of somewhat similar nature, further, it is likely that failure of synthesis of the enzyme activators may be quite as important as deficiencies in intake of their vitamin fractions Utilization would seem to rank equally with absorption as a major factor in the maintenance of health, and storage may be of equal importance

Little is known of riboflavin deficiencies in man but there is reason to think it may produce specific lesions Little attention has been given to andenylic acid, and it is likely that an abundant endogenous supply is constantly available from the breaking down of cell nuclei It is suggestive however, that

yeast and oral liver extract, which are highly curative for pellagra, are both potentially rich in nucleic acid from which ribose and andenylic acid can be derived Both yeast and liver, of course are very good sources of nicotinic acid Now that abundant supplies of nicotinic acid and riboflavin are available, the way is open for much more accurate observation, perhaps for the final solution of most of the problems of "B deficiencies" The great likelihood of the action of these vitamins as components of activating enzymes offers an excellent theoretical basis for the correlation of many apparently paradoxical phenomena Clinical progress must wait on refinements of biologic methods before many questions can be answered As yet, we do not know the distribution of nicotinic acid in body fluids, nor are there satisfactory methods for clinical assay of organs or secretions for them The relation of other components of the B complex to human disease is entirely obscure, and the effects of coincidental deficiencies of vitamins B_1, C, and A are not known

It is quite likely that the chronic annual relapsing endemic pellagra of the South is a more complex syndrome than alcoholic pellagra or pellagra produced in a relatively short time by experimental dietary restrictions especially when vitamins other than the B group are supplied in experimental diets The fulminating pellagra occasionally seen in patients maintained on parenteral glucose and salt solutions is a much closer parallel in that this represents total avitaminosis from intake plus rapid "burning out" of coferments by purely carbohydrate *source of energy*

A Study of 660 Cases of Pellagra—Pellagra has been a subject of interest in our clinic since 1919, and adequate records are available of 660 patients hospitalized during this twenty year period These seriously ill patients were those sent in as medical emergencies in many instances and were often moribund The annual admissions, deaths, and mortality percentages are shown in Chart 1 The group reflects the local economic situation only roughly The 1929 peak was surprising since no unusual financial stress was yet present in our community A much higher peak occurred during the past year and is obviously the result of cumulative malnutrition resulting

from prolonged unemployment of a considerable portion of the population Factors which will be discussed later seem to have caused wide fluctuation in the death rate

This record of twenty years may be divided into four periods, during which there was great variation in the theories regarding possible etiology of pellagra and a corresponding variation

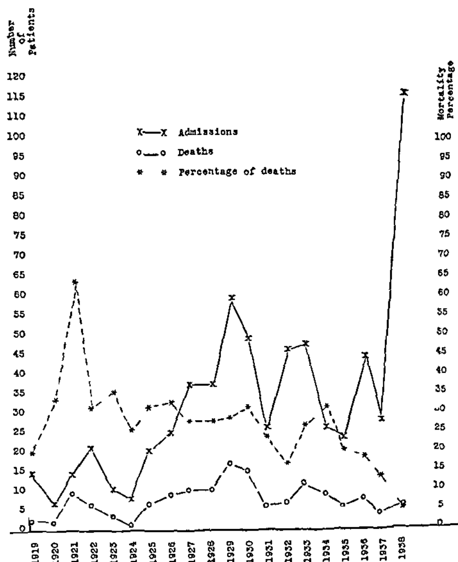


Chart 1

in the methods of treatment From 1919 to 1926 there was little constructive thought, the old idea of infection continued to be considered on account of the occurrence of fever, ulcerative lesions of the gastrointestinal tract, cachexia, and anemia with leucocytosis in a majority of patients Admissions for



Fig 31 —Cheilosis and dermatitis of the chin



Fig 32 —Dermatitis of hand same patient as Fig 31



Fig 33 —Dermatitis of perineum and thighs same patient as Figs 31 and 32

pellagra were few, and even the appallingly high death rate in 1921 was not a cause for great concern Investigations were largely hematologic and bacteriologic Treatment was empirical The patients were given a high caloric, high protein diet with the addition of 400 c c of tomato or citrus fruit juice, a liter of milk, 30 c c of cod liver oil, and at least 90 c c of dilute hydrochloric acid daily Many were tube fed, and dehydrated patients were given physiologic salt solution hypodermically and glucose solution intravenously Arsenic, as sodium cacodylate, and neoarsphenamine were used freely During this seven years 92 patients were treated, of whom 32 (33 7 per cent) died Goldberger's experiments at the Rankin County prison and at Spartanburg were discounted and some of the most eminent clinicians in the South denied that he had produced experimental pellagra

The Goldberger Period—During this same time Dr Goldberger and his associates were working at Milledgeville, and there were frequent visits to Augusta Early in 1926 Dr Goldberger suggested that all empirical treatment be abandoned and that all patients with pellagra be given a diet balanced in the sense of fulfilling metabolic requirements and with the addition of 90 Gm of dried brewers' yeast daily This suggestion was followed and during the nine years, 1926 to 1934, the pellagra curative diet had an approximate caloric value of 4000, representing 80 Gm of proteins, 400 Gm of carbohydrates, and nearly 200 Gm of fats It was prepared as liquid, soft, or solid diet and often administered by tube Not less than a liter of milk and 400 c c of citrus fruit or tomato juice were included This amount of food was often difficult to give even in eight feedings, and vomiting was frequent It was routine for vomited meals to be repeated Yeast was given suspended in milk, glucose and salt solutions were used extraorally in all dehydrated patients, and transfusions of blood were given those with serious anemias

During this nine years, 356 patients with pellagra were admitted to the hospital and 91 (25 56 per cent) died The improvement in the mortality rate over that of the era of empiric

treatment was only 8 1 per cent, and this in spite of the tremendous expenditure of effort During the last five or six years of this time liver extracts of various sorts were used in a rather haphazard fashion, being reserved for the most severe cases Not uncommonly patients showed startling improvement though the amounts given were usually inadequate in the light of later knowledge During 1934 the death rate rose to 33⅓ per cent, this was extremely discouraging and led to the decision to abandon all former methods of treatment and adopt an entirely experimental attitude toward the pellagra problem

Geographic Distribution of Endemic Pellagra —There were very many questions which seemed to need answers Many are by now at least partially solved, but five years ago they were urgent First, the geographic distribution of endemic pellagra seemed to require explanation On a map the area of high endemic incidence of pellagra almost exactly complements the area of high appearance of pernicious anemia The only important locality which does not conform to this distribution is Scandinavia where both diseases are prevalent

The region of high incidence of pellagra is that of excessive solar radiation in the temperate and subtropical zones that of high incidence of pernicious anemia is the region of deficient solar radiation in the north temperate and colder zones This matter of geographic distribution, apparently conforming to excessive solar radiation, seemed a promising lead until the fact of the low incidence of pellagra in the tropics was recognized More mature consideration of the question indicated that the *difference in food habits in the area was a much more likely* etiologic factor than intensity of sunlight

Pellagra —Another seemingly important factor was the negligible incidence of pellagra during the last years of the late war Here malnutrition was almost universal among the civilian populations, but pellagra was said to be of extremely rare occurrence Here again food habits seemed to be the determining factor The universal use of beer containing large amounts of yeast extractives probably acted as a potent preventive measure In apparent support of this hypothesis was the experience of British medical officers with prisoners of war in Egypt Pellagra was very infrequent among the Germans who had a beer

ration but was a plague among the Turks who had the same general diet but were from religion, total abstainers

Pellagra, Sprue and Pernicious Anemia.—*The question of the* possible relation of Addisonian anemia, sprue, and pellagra was given great consideration. Many others including Boggs and Padget, Spies, Castle and Rhoads in this country and Petri and Flinker in Europe, also concerned themselves with this problem. *The common occurrence of glossitis, achlorhydria, and* gastrointestinal disturbances in the three diseases is striking. Dermatitis is usual in pellagra, pigmentation, and a certain degree of atrophy of the skin in many patients in *pernicious* anemia and sprue.

Combined sclerosis is a usual feature of pernicious anemia, occurs infrequently in pellagra, and is very rare in sprue. Peripheral neuritis is not infrequent in pellagra but is rare in the other two diseases. Psychoses of a gross type are frequent in pellagra and but seldom seen in sprue and pernicious anemia, although *depression and personality changes* are not uncommon.

The blood in pellagra is seldom macrocytic and hyperchromic and the marrow is almost never hyperplastic. However, occasionally patients offer extreme difficulty in differential diagnosis, and we have seen two patients in whom typical Addisonian anemia developed after repeated attacks of pellagra. More suggestive even than apparent similarity in clinical manifestations was the fact that liver extracts are curative for *the three diseases*.

Because it seemed possible that some common factor might be active in production of the three syndromes, we undertook an experimental study of pellagra from the standpoint of its being *a conditioned deficiency. It was obvious from the* inception of this work that the factors involved were not identical with those of pernicious anemia. Spies and Payne and Saleh have shown that the achlorhydric gastric juice of pellagrins contains the intrinsic substance of Castle. We have been able to show that the fatty liver of a pellagrin is a good source of the hematopoietic substance but is entirely lacking in that which cures pellagra. Helmer and his associates have shown that the *gastric mucosa in pernicious anemia* and in pellagra

is deficient in digestive ferments We have been convinced that the deficient gastric function of the great majority of pellagrins is of significance, and that cure and relapse have a definite relationship to the persistence of achlorhydria or to regeneration of gastric function. In this respect pellagra differs profoundly from pernicious anemia in which treatment seems never to have any influence on gastric function In pellagra the prompt recurrence of symptoms on cessation of treatment and the presence of irreversible achlorhydria seem constantly associated This led to the hypothesis that pellagra might result from intrinsic defect as well as from extrinsic deficiency

Seasonal Incidence and Age Distribution —Prior to the beginning of the experiment the records of 440 patients were analyzed in an effort to find some promising line of investigation as well as to clarify our own impressions The same data have been set down for 220 patients observed during the experimental period

Seasonal incidence was in accord with general experience Over half of all patients were admitted during the months of May, June and July with the annual peak in July Pellagra was seen throughout the year however, and during the past two years there has been a relative increase in winter admissions

Age distribution was wide, pellagra being observed at all ages, between five and ninety two years Sixty per cent of the patients were grouped in the three decades, twenty one to fifty years Thirty two per cent of the patients were men and 68 per cent women There was no significant racial variation in sex incidence

Race —Although our patients were drawn from a population almost exactly divided between the races, 57 per cent were white and 43 per cent colored This discrepancy may seem surprising in view of the generally low scale of living of Southern negroes In our experience it was to be expected Very many negroes are in domestic service and eat the same food as their employers Frequently a considerable amount of this food finds its way to the servant's home Many other negroes are parasitic on white families for whom they may once have worked, and they regularly solicit food or money which is sel

dom denied As a result they are more likely to eat meat and fish than they are to indulge in sweets or other luxuries

Another factor which may have some bearing is the racial fondness for liver, kidneys, and spleen which are certainly eaten much more often than by white people In addition to this, they have small scruples about stealing and none about begging when in need, so that the lot of the *poorest negro* is seldom as hard as that of the poor white with his more highly developed *inhibitions*

The death rate during the two decades was 22 12 per cent, but there was a marked difference between the races, of 376 white patients 17 8 per cent died, while 26 7 per cent of the 284 negroes died This discrepancy can possibly be accounted for by the large number of *neglected senile negro patients*, many of whom were moribund on admission Syphilis and *tuberculosis were also much more* frequent and lymphogranuloma was confined to the negro patients

Symptoms —The incidence of cardinal symptoms and signs of pellagra is set down in Table XIII No significant differences between the groups of patients and those who died are apparent, except in the frequency *of psychoses and fever* Psychosis of some type occurred in 48 per cent of the entire group, but *in 78 per cent of those* who died, while fever of over 100° occurred, nearly three times as often in patients who did not recover

TABLE XIII

NUMERICAL AND PERCENTAGE INCIDENCE OF SIGNS OF PELLAGRA IN 660 PATIENTS

	PATIENTS WHO RECOVERED (514)		PATIENTS WHO DIED (146)	
	NUMBER	PER CENT	NUMBER	PER CENT
Glossitis and stomatitis	508	97	143	98
Dermatitis	473	92	143	98
Diarrhea	349	68	111	76
Psychoses	206	40	111	76
Fever over 101 F	128	25	95	65

The Blood —Considerable importance was attached to examination of the blood, but methods and criteria varied considerably, since the period covered by these observations has been one of great advance in hematologic technique Estimations of blood sugar and nonprotein nitrogen were made in 600 instances

and nothing of significance was noted Hemoglobin determinations were made by Sahli, Newcomer, or Briggs' modification of the Osgood Haskins method on the blood of 640 individuals, erythrocyte and leucocyte counts were made on the same number Anemia was considered present when the hemoglobin was below 80 per cent Sahli or 12 Gm per 100 c c by other methods, and the erythrocyte count below 4,000,000

In many cases anemia was masked on admission by dehydration, 84 per cent of the group was anemic by these criteria, and in 28 instances (4 25 per cent) the anemia was hyperchromic Leucopenia was found in 10 per cent of the group, and white cell counts above 10,000 in 48 per cent

Stomach Contents—During the last ten years we have attached much importance to the stomach contents as an indicator of adequate gastric function Test meals were done on 446 of the patients in this series Prior to 1934 the Ewald meal or the alcohol test meal, suggested by Bloomfield, was used During the past five years histamine has been used in all cases By these various methods, 77 3 per cent of pellagrins showed achlorhydria, and in the remaining 22 7 per cent, the gastric contents were quite regularly small in volume and seldom showed free hydrochloric acid values of over 25 degrees There seemed to be a very significant relation between the presence of free hydrochloric acid in the gastric secretion and cure, relapse and death Of the 108 patients who had free hydrochloric acid, only 8 (7 4 per cent) died, while in the group of 338 with achlorhydria, there was a mortality of 19 5 per cent Two hundred and fourteen patients had no gastric analysis Many of these were so ill that it seemed inhuman to subject them to the procedure, and many others were admitted during the first ten years of the record before the importance of these tests was appreciated Of this group 29 7 per cent died The high mortality reflects the extreme condition of many of these individuals

Neurologic Manifestations—Neurologic disturbances, other than psychoses, were not frequent, and in this respect our statistics are in wide variance with those of other observers Some evidences of combined sclerosis were found in 40 patients (6 per cent), and persistent peripheral neuritis was seen in 15

(2.3 per cent). The very low incidence of neuritis is probably related to the rarity of alcoholics among our patients. Alcohol as an etiologic or precipitating factor was relatively insignificant. A history of alcoholism was obtained from 54 (8.2 per cent), and this group included 13 of the instances of peripheral neuritis.

Intrinsic Factors.—The frequency of achlorhydria and the common occurrence of anemia caused us to decide to try to determine the presence or absence of any "intrinsic factor" in pellagra. The methods of control of our experiments were similar to those commonly used by other students of pellagra. Patients were kept in bed at rest and given a diet very low in known curative substances; the diet used was a modification of the Goldberger-Wheeler diet and contained no added nutritional adjuncts. We felt and still feel that such a diet more accurately reproduces that commonly used by persons developing pellagra than does one lacking only a single vitamin. Our routine pellagra producing diet is shown in Table XIV. The diet is bulky and of adequate caloric value.

TABLE XIV

BASAL PELLAGRA PRODUCING DIET

FOOD	GRAMS	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Corn meal, white	300	25.0	3.3	235	1095
Cowpeas, dried	45	11.0	0.8	28	162
White flour	30	4.0	0.3	25	118
Lard or cotton seed oil	45	0.0	45.0	0	405
Karo syrup	190	0.4	0	140	562
Fat salt pork	30	0.5	24.0	0	216
		40.9	7[illegible].4	428	2558

Diets.—In certain instances the "maize diet" of Spies has been used. This consists of 500 Gm. of white corn meal cooked into mush and served plain, fried, or baked with syrup, and coffee as desired. In special cases rapid relapse has been brought about by pure glucose and water regimen, 300 to 500 Gm. of glucose orally and parenterally being given during twenty four hours. A considerable number of pellagrins recover on the basal diet.

During the present investigation, 29 (13.1 per cent) had complete symptomatic cures. Curative diets were the same

that we had used for a number of years and differed in no significant detail from those of Spies, Chinn, and McLester In a few cases, when the patients were seriously and alarmingly ill, the curative diets were used for maintenance, yeast being omitted and the test substance used to replace it

Suitable groups of controls were fed the curative diets and a considerable number of patients, for various reasons, received no special treatment, usually on account of very brief stay in the hospital

The blood, urine, and gastric contents after histamine were examined in all patients at weekly intervals The stools were searched for parasites X ray examinations of the lungs and gastrointestinal tracts were made and electrocardiograms obtained When possible the weight was determined at weekly intervals Intercurrent infections were treated by the usual methods In a large number of the patients the urine was tested by the "first method of Hans Fischer" for what was believed to be porphyrin but has since been shown to be some other reacting substance

Gastric Intrinsic Factor Studies—The first experiment was an imitation of those of Castle and his associates on pernicious anemia Castle's technique could not be followed entirely because the administration of large amounts of digested beef would have furnished a known adequate supply of pellagra-curative substances Normal human gastric juice obtained from volunteers was used The method was to secure all the gastric juice secreted by a fasting subject during the hour following the injection of 0 75 mg to 1 mg of histamine It was immediately refrigerated and given to patients on the day of collection

The gastric juice was given in amounts of 240 c c daily in a single dose five hours after the evening meal This was done to eliminate the factor of increased digestion of food which might have been brought about by any other method of administration The gastric juice, ice cold and flavored with synthetic lemon extract, was taken well Treatment was continued for ten days except in one instance when it was given for forty nine days

Ten patients were thus treated One seemed moribund on admission and remained stuporous and febrile for fifty one days when death occurred from no obvious cause She was so se

verely ill that all known curative substances were given. Feeding was always by tube: liquid curative diet with 45 Gm. of yeast, 10 Gm. of ventriculin, 90 c.c. of Valentine's liver extract, and 3 c.c. of Lilly's extract "343" were given daily, and for forty-nine of the fifty-one days 100 to 300 c.c. of gastric juice. Dermatitis, glossitis, and stomatitis healed rapidly; diarrhea was only moderately improved, and the patient remained incontinent.

Another patient who had shown rapid improvement, with cure of glossitis, stomatitis, vaginitis, dermatitis, and diarrhea within eight days and whose pellagra, therefore, seemed satisfactorily cured, died suddenly of acute heart failure, possibly coronary occlusion, the seventeenth day after admission. The other 8 patients showed rapid and remarkable improvement in all signs and symptoms, clinical cure being accomplished on the sixth to tenth days of treatment. Glossitis and stomatitis were first relieved, usually during the first forty-eight hours, diarrhea decreased rapidly, and dermatitis was the last sign to be favorably affected. The appetite improved on the second to fourth days of treatment, and the appearance of free hydrochloric acid in the gastric contents was noted in 5 of the 8 surviving patients.

We were greatly intrigued by the results obtained in this small group. Cure of the mucosal lesions, regeneration of the lingual papillae, and resolution of dermatitis were quite as rapid as we have come to expect in patients adequately treated with nicotinic acid. Conclusions are hard to draw. No satisfactory method of estimating nicotinic acid or its compounds in gastric juice has yet been found. Whether gastric juice acts as a curative agent on account of a relatively high nicotinic acid content or whether it actually furnishes an "intrinsic factor," which is necessary for the utilization or synthesis of minimal amounts of nicotinic acid in the diet, is a problem which still remains unsolved. The patient who lived so long under intensive treatment with all of the known curative substances, yet finally died, probably represents the extreme type of irreversible pellagra with advanced damage to the central nervous system as well as to the gastrointestinal tract.

Svend Petri has used gastric juice in the treatment of pellagra and of what he considered a pellagrous syndrome in dogs

produced by surgical removal of the stomach The results were excellent but, unfortunately, the patients with pellagra were not adequately controlled They had ward diet and, strangely enough, a teaspoonful of yeast was added to the gastric juice with which they were treated We feel that no conclusions can be drawn from his experiments Robert Flinker has also suggested an intrinsic deficiency in pellagra and elaborated the hypothesis in a most satisfactory manner He, however, has not published any experimental data

Extracts From Pigs' Stomachs—The use of human gastric juice proved exceedingly laborious Not only was much time consumed in its collection but the most enthusiastic donor tired of the frequent intubations and other various discomforts attending the administration of histamine Since the gastric juice of pigs has been found quite similar to that of human beings we proposed to use it as a substitute Great difficulty was encountered in securing a satisfactory juice although we had full cooperation of the operators of abattoirs, nearly all the pigs' stomachs contained large amounts of food or filth from which it was not possible to separate the gastric juice Each day a few stomachs could be found which were empty of food and relatively clean It was possible to secure enough clear juice to treat two patients with amounts of 200 c c daily over ten day periods

The pigs' stomachs were emptied into clean flasks, the contents taken as rapidly as possible to the laboratory, filtered and refrigerated, and administered by the same technique employed for human gastric juice The two patients who were treated made rapid and uneventful recovery, paralleling that of those who secured cure under the treatment of human gastric juice

It seemed impractical to continue experiments with this substance so it was decided to test the potency of extract of pigs' stomachs The stomachs were opened and emptied at the abattoir, brought quickly to the laboratory, and while still warm they were thoroughly washed in water, and then with ice cold 2 per cent sodium bicarbonate solution to remove adherent mucus The mucosa was rapidly stripped, put twice through a meat chopper, and the resulting pulp was suspended in four volumes of ice cold physiologic salt solution This mixture was

shaken mechanically for twenty minutes and then refrigerated over night The following morning the opalescent supernatant fluid was decanted, filtered, and again refrigerated The original mucosa pulp was cultured to determine the presence or absence of pathogenic bacteria and examined microscopically for trichinella larvae The extract prepared was almost odorless and tasteless It showed no free HCl, and the average pH was 5 3, the total acidity 3 8°, total nitrogen averaged 110 mg per 100 c c, and the total protein calculated from this was 692 mg per 100 c c Rennin and pepsin were present in considerable amounts which varied much more than the pH or the nitrogen content in different batches

Seven patients were treated with this preparation which was given in amounts of 300 c c daily, representing 60 Gm of fresh mucosa This, too, was given in one dose five hours after the evening meal All the patients showed remarkably rapid improvement comparable in all respects to that seen in those treated with human or porcine gastric juice Glossitis, stomatitis, and diarrhea were cured during the first thirty six to forty eight hours of treatment, and by the fourth day there was quite regularly marked improvement in dermatitis

Four patients in succession made dramatic recoveries, with reappearance of free HCl in the gastric juice The fifth patient developed bronchial pneumonia on the sixth day of treatment and, although signs of pellagra were in abeyance, died in twenty four hours The sixth patient showed the usual clinical improvement but no return of free HCl in the gastric contents, so treatment was continued for fifteen days when an astounding relapse occurred Within twenty four hours glossitis and stomatitis became severe, there was an acute vesicular dermatitis on the hands and feet, with diarrhea, fever, and delirium

Blood and stool cultures were negative for pathogenic organisms, and stools were searched for trichinella with negative results Liquid curative diet containing 90 Gm of yeast was started immediately, and 20 c c of liver extract were given intravenously three times daily In spite of these measures, stomatitis and glossitis progressed, and the skin over the hands, feet, and genitalia sloughed Death occurred on the seventh

day of relapse Autopsy was not obtained The seventh patient was extremely ill, with unusually severe glossitis, dermatitis, and fever on admission Treatment with pigs' mucosa extract was begun on the third day of hospitalization and improvement in all symptoms and signs was remarkable Glossitis, diarrhea, and fever disappeared after forty eight hours On the eighth day the patient seemed almost well On the ninth day a relapse occurred similar in all respects to that described in the preceding case Temperature rose rapidly to 103° F, with delirium, frequent watery diarrhea, and the most acute type of ulcerative stomatitis, glossitis, and dermatitis Treatment was as in the preceding case except that four doses of liver extract were given intravenously each day This man lived, febrile and delirious, with no definite improvement in any of his manifestations, for ten days, and death occurred suddenly Again it was impossible to secure an autopsy

The remarkable, fulminating, fatal relapses in these two patients who had made spectacular improvement led us to abandon pigs' mucosa extract The mechanism of relapse is not clear though some very definite factor must be involved The mode of death was that ordinarily seen in the known severe type of endemic pellagra, and it is possible that the mucosa extract contained some substance which caused alteration of some important metabolic process

Endogastrin —The next material to be tested was a desiccated, defatted preparation of pigs' gastric mucosa ("Endogastrin") made for experimental use by E R Squibb and Sons and proposed by Greenspon for the treatment of pernicious anemia It seemed to us that this substance offered all that the pigs' mucosa extract could, with the greater advantage of known sterility and small bulk It was dispensed in capsules, each of which represented 5 Gm of fresh pigs' mucosa The method of preparation seemed to obviate the problem of destruction of any active factor Seven patients were treated with endogastrin The amount used was three capsules three times a day, representing 45 Gm of fresh pigs' mucosa All of these patients were severely ill

The results with endogastrin were again spectacular In each case glossitis, stomatitis, and diarrhea were cured within forty

eight hours, and there was rapid resolution of the dermatitis Four patients were cured in ten days, three of whom showed regeneration of free HCl in gastric juice

One patient, who was severely demented, took endogastrin for twenty four days with complete healing of all lesions but no improvement in the mental state, developed bronchopneumonia, and died after four months of hospitalization At autopsy no lesions of pellagra were evident, though detailed histologic study of the brain showed degenerative changes

Another patient who had apparently recovered after ten days of treatment developed severe pyelonephritis and died but without relapse of pellagra The last patient treated behaved exactly as did the two who died after the treatment with pigs' mucosa extract On the eighth day of endogastrin, after rapid cure of all signs of pellagra during the first four days of treatment, she rapidly became febrile and delirious, with diarrhea (10 stools during the first twenty four hours) During the first twenty four hours of relapse, severe ulcerative stomatitis and glossitis with vesicular dermatitis of the hands, feet, and perineum developed She was given intensive treatment with yeast and intravenous liver extract but died on the fifth day of relapse Since this patient's course was in all respects similar to that of those who relapsed on pigs' mucosa extract and since no adequate explanation for these shocking occurrences was found, no further experiments with mucosa preparations were carried out It seemed evident that there was great virtue in them, for rapid cure of all the acute lesions was obtained in every case

We feel certain that ferment action and protein content played no part in the cure It has not been possible to determine the presence or absence of nicotinic acid in pigs' mucosa extract prepared by the same technique or in the samples of endogastrin which are still in our possession Again the question of an intrinsic factor remains unsettled Still more important seems the question of the mechanism of apparently irreversible relapse, for we have seldom seen patients with even the severest spontaneous pellagra who failed entirely to respond to the methods of treatment applied in these cases

Ventriculin—Concurrently with these experiments some patients were treated with various substances other than direct gastric derivatives, ventriculin, and autolyzed liver preparation made by E R Squibb and Sons, various liver extracts, and some crude and refined vitamin preparations were employed Ventriculin, in amounts varying from 90 to 300 Gm per day over a period of ten days, was used in the treatment of 4 patients, all of whom made rapid and uneventful recovery While we feel that the presence of gastric mucosa in this preparation was of extreme importance, the added protein and unknown nutritional factors made the experiment unsatisfying from the point of view of specificity Spies had already proved the curative property of large doses of ventriculin, and our trial of it was only to satisfy ourselves of its value Four patients were given autolyzed liver in doses of 15 Gm three times a day for ten days These patients also made rapid and apparently complete recovery Two, however, remained achlorhydric and later relapsed

Liver Extracts—Liver extract of various sorts was used in the treatment of 45 patients, 10 were given no other curative substance In 35 instances it was used as accessory or salvage therapy in patients with severe relapse or in those who failed to respond to other treatment In our experience, the liver extract preparation for intravenous administration has been the most actively curative substance used, except nicotinic acid Oral and intramuscular administration have given relatively slow improvement

Of the patients treated exclusively with liver extract, 3 were given Valentine's extract for oral administration in doses of 30 c c three times daily for ten days All showed good improvement, requiring three to five days for cure of stomatitis, glossitis, and diarrhea, and seven to ten days for marked improvement of dermatitis

Intramuscular injections of Lilly's "343," 3 c c daily for 10 days, were employed 4 times with results comparable with those of oral administration of aqueous extract of liver One patient regained free HCl in the gastric juice Three patients were given no curative treatment, except 20 c c liver extract

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Another patient who had apparently recovered after ten days of treatment developed severe pyelonephritis and died but without relapse of pellagra The last patient treated behaved exactly as did the two who died after the treatment with pigs' mucosa extract On the eighth day of endogastrin, after rapid cure of all signs of pellagra during the first four days of treatment, she rapidly became febrile and delirious, with diarrhea *(10 stools during the first twenty-four hours) During the first* twenty four hours of relapse, severe ulcerative stomatitis and glossitis with vesicular dermatitis of the hands, feet, and perineum developed She was given intensive treatment with yeast and intravenous liver extract but died on the fifth day of relapse Since this patient's course was in all respects similar to that of those who relapsed on pigs' mucosa extract and since no adequate explanation for these shocking occurrences was found, no further experiments with mucosa preparations were carried out It seemed evident that there was great virtue in them, for rapid cure of all the acute lesions was obtained in every case

We feel certain that ferment action and protein content played *no part in the cure It has not been possible to determine* the presence or absence of nicotinic acid in pigs' mucosa extract prepared by the same technique or in the samples of endogastrin which are still in our possession Again the question of an intrinsic factor remains unsettled Still more important seems the question of the mechanism of apparently irreversible relapse, for we have seldom seen patients with even the severest spontaneous pellagra who failed entirely to respond to the methods of treatment applied in these cases

Ventriculin —Concurrently with these experiments some patients were treated with various substances other than direct gastric derivatives, ventriculin, and autolyzed liver preparation made by E R Squibb and Sons, various liver extracts, and some crude and refined vitamin preparations were employed Ventriculin, in amounts varying from 90 to 300 Gm per day over a period of ten days, was used in the treatment of 4 patients, all of whom made rapid and uneventful recovery While we feel that the presence of gastric mucosa in this preparation was of extreme importance, the added protein and unknown nutritional factors made the experiment unsatisfying from the point of view of specificity Spies had already proved the curative property of large doses of ventriculin, and our trial of it was only to satisfy ourselves of its value Four patients were given autolyzed liver in doses of 15 Gm three times a day for ten days These patients also made rapid and apparently complete recovery Two, however, remained achlorhydric and later relapsed

Liver Extracts —Liver extract of various sorts was used in the treatment of 45 patients, 10 were given no other curative substance In 35 instances it was used as accessory or salvage therapy in patients with severe relapse or in those who failed to respond to other treatment In our experience, the liver extract preparation for intravenous administration has been the most actively curative substance used, except nicotinic acid Oral and intramuscular administration have given relatively slow improvement

Of the patients treated exclusively with liver extract, 3 were given Valentine's extract for oral administration in doses of 30 c c three times daily for ten days All showed good improvement, requiring three to five days for cure of stomatitis, glossitis and diarrhea, and seven to ten days for marked improvement of dermatitis

Intramuscular injections of Lilly's "343," 3 c c daily for 10 days, were employed 4 times with results comparable with those of oral administration of aqueous extract of liver One patient regained free HCl in the gastric juice Three patients were given no curative treatment, except 20 c c liver extract

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for intravenous use once daily All made spectacular recoveries Oral lesions were cured during the first thirty six hours, diarrhea stopped on the second day, and dermatitis was healed by the fifth or sixth day No deaths occurred in this group of liver treated patients

In the remaining 35 patients treated with liver extract, the intravenous preparations were used in amounts varying from 20 to 80 c c daily This expensive method of treatment was reserved for the more severely ill patients, and almost incredible results were obtained with numerous apparently moribund cases, though there were 7 deaths in the group While this mortality of 20 per cent is not good, we are certain that no other



Fig 34 — Tongue relapse" in patient whose requirement of nicotinic acid was 600 mg daily three days after, dosage was reduced to 500 mg

method of treatment would have been so successful and even now we employ liver extract intravenously when occasional patients do not respond well to nicotinic acid

Nicotinic Acid Content of Liver —Our interpretation of cure with ventriculin and various extracts of liver has been that a substance specifically curative for pellagra and probably a "compound" of the intrinsic and extrinsic factors analogous to the hemopoietic substance is present in them In the light of present knowledge, the question of the nicotinic acid content of these preparations is an urgent one, but no adequate method of chemical assay has yet been devised Liver may contain as much as 25 mg of nicotinic acid per 100 Gm, but the curative

results obtained with liver extract have been much more striking than those with nicotinic acid in the hypothetically equivalent amounts

Another interpretation might be that adjuvant substances may be present which act as catalysts for the specific vitamin It seems very likely that the substances curative for pellagra are stored in the liver Whether this is nicotinamide or some other compound of nicotinic acid remains to be determined Riboflavin may also be a storage substance of importance Various other investigators have emphasized the value of liver and liver extract in the cure of pellagra, notably Boggs and Padget, Magness and Ramsdell, Spies and his associates, and Smith and Ruffin

Liver Extract From Pellagrous Liver—We have for many years been impressed by the uniformly fatty liver of fatal pellagra, as knowledge of the probable etiologic mechanism of the disease has been clarified, the significance of this finding has seemed to be more important Lately the opportunity for testing the definite potency of an extract of pellagrous liver has been presented It was possible to secure the liver of a person dead of uncomplicated pellagra who had had absolutely no treatment This liver was secured within two hours of death and was refrigerated until thoroughly chilled, and from it the "G fraction" was successfully prepared

This extract was given intravenously in doses of 25 c c representing 100 Gm of liver, for two days, to a patient with typical Addisonian anemia, and the same amount to two patients with a relapse of pellagra The patient having Addisonian anemia showed a prompt reticulocyte response within forty eight hours after the first dose The reticulocytes reached a peak of 14 per cent on the fifth day, and there was the usual increase in red blood cells and hemoglobin The two patients with pellagra showed no response whatever, becoming rapidly worse, and both required urgent treatment with large doses of intravenous commercial liver extract

Histologic examination of the liver used showed extreme fatty degeneration This experiment seemed to show conclusively that the pellagra curative factor in liver extract is quite different from that concerned with hematopoiesis

Vitamin Concentrates—During the two years of these experiments, certain vitamin concentrates were *employed in selected* cases An extract of rice polishings (ryzamin B), furnished by Burroughs Wellcome Co, was given *to 7 patients* The preparation is rich in vitamin B_1, and contains considerable amounts of the B_2 complex It was administered in amounts of 45 Gm daily There was no spectacular response comparable to that following treatment with liver and stomach preparations, but gradual, slow improvement in all pellagrous manifestations required ten to fourteen days to produce symptomatic cure Only two of the group showed regeneration of free HCl in the gastric juice It seemed evident that this substance contained pellagra *curative principles* but was *not an optimal one for treatment* of pellagra

Riboflavin Deficiency—*Riboflavin* became available at this time and was given to 4 patients The dose was small, 3 mg daily, intramuscularly, over a period of five days No definite improvement was observed and other methods of treatment were later employed

Recently interest in riboflavin has been stimulated by Sebrell's observation that marginal stomatitis or "cheilitis" can be cured by it As yet the matter of a definite clinical sign of riboflavin deficiency remains unsettled

Carotene—Because Mellanby had reported animal experiments which seemed to indicate that vitamin A, or carotene, was protective, for the central nervous system, against the effects of "B_2 deficiency," carotene in doses of 9 mg daily was given to 3 patients for ten days These patients were actively demented and they were given no other treatment at the time, no effect was observed

Curative Diets—As stated above, 19 patients were treated with curative diets This group was definitely composed of patients with milder manifestations of pellagra and those subjected to experimental conditions One death from bronchial pneumonia occurred in this group Cure was quite regularly slow as compared to that produced by stomach and liver preparations

The usual time required for disappearance of glossitis and diarrhea was four to six days Later improvement, however

was rapid and steady Six of these patients had some amount of free HCl in the gastric contents Nine of the remaining 13 showed return of free HCl after treatment Twenty nine patients became free from all signs and symptoms on the basal pellagra producing diet

Recovery was always slow but progressed in the same fashion as that seen under treatment with curative substances Glossitis, stomatitis and diarrhea were cured in the order named, dermatitis often required two to three weeks for resolution Eighteen of these patients showed low normal values for free HCl in the gastric contents on admission Of the other 11 who were achlorhydric, 5 regained some degree of free acid while under observation

There are various possible explanations of recovery on pellagra producing diet Quite frequently the food is much better in quality and quantity than the patient's habitual diet, and in the presence of even partially adequate gastric function, sufficient curative substance may be extracted from it to cause remission Rest in bed, with lowering of metabolic requirements, is probably important to a degree not commonly appreciated

Sunlight —Protection from sunlight is a factor insisted upon by some observers but not considered important by me

In our experience, sunlight is of little specific effect in precipitating the dermatitis of pellagra and still less active in producing mucosal lesions In some patients any physical or chemical irritant will cause dermatitis, frequently heat, strongly alkaline soap, or the fumes of acids may produce a typical eruption

It is most likely that genital lesions are the result of irritating discharges or of putrefying sebaceous secretions in unclean individuals The effects of ultraviolet and infrared rays are not denied, but we do deny any specificity for such agents It is common experience to see the most severe type of dermatitis in patients subjected to experimental relapse while remaining in the hospital in a poorly lighted ward

Pellagra Following Exposure to X ray —In this connection it may be worth while to mention a patient in whom severe pellagra followed heavy exposure to x ray This woman was ad

mitted for the symptoms of mediastinal pressure and was found to have Hodgkin's disease Following the administration of 600 R U to the mediastinum she developed severe, acute pellagra with vesicular and ulcerative dermatitis of the hands, elbows, genitalia and feet, ulcerative glossitis and stomatitis, fever, delirium and diarrhea There was achlorhydria and rapidly developing anemia All symptoms and signs were fully developed seventy two hours after the last x ray treatment She was cured with liver extract, 80 c c were given intravenously, daily, for three days She showed rapid restoration of gastric function and, though kept under observation for thirty days on pellagra producing diet, remained apparently well

Nicotinic Acid in the Treatment of Pellagra —Our efforts to show *that pellagra is a condition deficiency were abruptly* interrupted by the discovery that nicotinic acid is curative for black tongue in dogs and, by analogy, for human pellagra Therapeutic trial of nicotinic acid was begun in October, 1937, and has continued to the present time

One hundred twenty five hospital patients and approximately twice this number of ambulatory patients have been treated and maintained with nicotinic acid The specificity of this vitamin in the cure of stomatitis, glossitis, and psychic disorders cannot be overemphasized

The behavior of gastric function on nicotinic acid treatment closely parallels that under liver therapy A certain number of patients regain some degree of free HCl in the gastric contents quite rapidly These are cured and do not soon relapse Others are relieved of all symptoms and signs but remain achlorhydric and relapse quickly when nicotinic acid is withdrawn or when a submaintenance dose is given

Dermatitis has healed slowly, more slowly than when yeast or liver extract was used, and there is reason to suppose that factors other than nicotinic acid may be concerned The response of gastric function to this method of treatment seems to strengthen the hypothesis that an intrinsic defect may be important in the pathogenesis of pellagra It was not to be denied that an apparently intrinsic deficiency may be due to lack of absorption or of storage

Dosage of Nicotinic Acid.—We have been unable to establish any routine dose of nicotinic acid; some patients are cured by as little as 50 mg a day given by mouth, and others have required as much as 1,800 mg per day. When intravenous administration is used, we are sure that the amount necessary is smaller; very many patients have been cured by 100 mg intravenously for three days, and others have required as much as 600 mg.

Occasionally patients have not responded to nicotinic acid but have been cured by liver extract given intravenously. Two patients were found who fulfilled all the criteria for the diagnosis of Addisonian anemia but failed to show any response to intensive therapy with liver extract intramuscularly. Since these patients had histories of recurring attacks of pellagra in the past, nicotinic acid was tried. Three hundred milligrams were given intravenously daily for three days, after which 100 mg were given daily by mouth. Both patients showed rapid increase in red cell count and hemoglobin, with return of blood to normal quantity and volume indices within three weeks, and there was simultaneous disappearance of the signs of combined sclerosis. At no time was there any striking reticulocyte response, the highest counts being 4 and 5 per cent, respectively. Both patients recovered some degree of HCl in the gastric juices. This response to nicotinic acid was entirely unexpected and awaits explanation.

Nicotinic Acid in Stuporous Patients.—Peculiar interest is attached to a group of stuporous patients showing no definite signs of pellagra who have responded to nicotinic acid by rapidly regaining consciousness (Figs. 35 and 36.) Some 21 patients with unexplained stupor have been admitted during the past six months. Eighteen of these were elderly, arteriosclerotic individuals whose condition formerly would have been diagnosed as stupor from cerebral arteriosclerosis or "cerebromalacia." The remaining 3 were relatively young individuals between the ages of 30 and 40 years. Five of the group did have fiery red tongues as a suggestive sign of vitamin deficiency. Nicotinic acid in doses of 100 to 300 mg., intravenously, each day for three days, restored all these patients to consciousness, and all were

dismissed apparently cured. In many there was amazing response to the first dose of nicotinic acid, some regained consciousness within an hour from the time of injection. It has been suggested by Jolliffe that stupor may be a specific sign of nicotinic acid exhaustion.



Fig. 35.—Atrophic red tongue of stuporous patient, showing no other evidence of pellagra. Patient recovered rapidly on nicotinic acid.



Fig. 36.—Rough coated tongue of stuporous patient with no evidences of pellagra. Patient recovered rapidly on nicotinic acid.

Multiple Vitamin Deficiencies.—The possible relation of the other vitamins to the syndrome of pellagra is the subject of present study. It seems highly improbable that clinical pellagra is ever the result of deficiency in a solitary nutritional factor. All of our pellagrins who have been subjected to adequate study

have been deficient in vitamins A and C Some few have later been given large doses of riboflavin in an effort to confirm Sebrell's suggestion that cheilitis is due to deficiency of this substance We have seen one instance of resolution of severe dermatitis under heavy riboflavin therapy, and we have seen one instance of marked improvement of cheilitis In our experience, endemic pellagra seems to be a polyavitaminosis of which the definitive signs and symptoms are probably due to nicotinic acid deficiency Anemia, certain types of dermatitis, and stomatitis may have other causes

Gastric and Liver Intrinsic Factors—Continued starvation for the essential extrinsic vitamin or vitamins results, we believe, in changes in the gastric mucosa, the liver, and central nervous system which may become irreversible These changes so condition the primary vitamin deficiency that cure, remission, and relapse may be so largely governed by them as to be predicted with considerable accuracy

The most important of the conditioning factors seems to be atrophy of the gastric mucosa with failure to produce digestive ferments and HCl What other functions may be impaired we do not know Later fatty infiltration or degeneration of the liver occurs, probably with loss of ability to synthesize a substance necessary for the prevention of pellagra This hypothetical substance seems likely to be nicotinamide, and there may be a coincident disturbance of hematopoiesis of a different order from that present in Addisonian anemia and curable with nicotinic acid but not with the G fraction of liver The neurologic phenomena of pellagra may appear in the absence of changes in the skin or mucous membranes but seem always associated with achlorhydria

Pellagra presents many phenomena analogous to pernicious anemia and sprue and may represent a deficiency complex closely related to both In pernicious anemia, gastric dysfunction is apparently of primary importance and may be a constitutional or congenital defect Failure of elaboration of intrinsic substance results in failure in synthesis of the essential hematopoietic factor, with resulting changes in the bone marrow and central nervous system

The blood examination showed hemoglobin 14.5 Gm., red blood cells 4,800,000, white blood cells 6,050, total nonprotein nitrogen 29.5, glucose 91, cholesterol 213, and chlorides 485. The basal metabolic rate was -7. Analysis of an Ewald meal revealed free hydrochloric acid 6, total acidity 22. X-ray examination of the gastrointestinal tract was entirely negative. There was a trace of blood in the stools on one occasion. No amebae were found, although a single cyst had been reported a year previously. Because of the possibility that this was a case of atypical Simmonds' disease she was given 1 c.c. of polyansyn intramuscularly daily. The glossitis promptly disappeared and the diarrhea improved. By February, 1940, she had gained 13 pounds, the most she has ever weighed.

The patient has since then become less emotional, is able to take care of a four room apartment, and resume normal social activities. Her menstrual periods are less painful and have a more normal flow. Nevertheless, during each menstrual period and the week thereafter there is a moderate to severe return of the diarrhea. Recently 2 c.c. of polyansyn daily during the week preceding the menstrual period greatly decreased these recurrent diarrheas. If the polyansyn is stopped the symptoms return within two weeks.

In view of the prompt recovery of the glossitis following the use of an extract of the anterior lobe of the pituitary gland, it appeared rational to apply this therapy to persons with pellagra who had failed to respond to the administration of large amounts of nicotinic acid, riboflavin, liver parenterally, and adequate diets.

CASE 3.—C. N., a white male laborer, aged 49 years, entered the Cook County Hospital on August 29, 1939. His immediate complaints were epigastric pain for the past year, loss of appetite for six months, and a loss of 50 pounds during the past year.

The epigastric pain had no relation to meals, although he occasionally vomited about one hour after a meal. He had a diarrhea of four to five liquid stools daily.

The essential physical findings were emaciation, a severe glossitis (a red beefy tongue), and a sore reddened pharynx.

The results of laboratory examinations showed that the urine contained a two plus sugar and a three plus albumin. An Ewald meal revealed an achlorhydria. No parasites nor blood were found in the feces.

A glucose tolerance test showed fasting glucose 106, at 9 A.M., 272, 10 A.M. 200, 11 A.M. 158.

The blood examination revealed hemoglobin 10 Gm., red blood cells 3,590,000, white blood cells 4,800, total nonprotein nitrogen 23, cholesterol 135, cholesterol esters 36, and phosphatase 7.38. The Kahn reaction was negative. The basal metabolic rate was -11.

X-ray of the gastrointestinal tract revealed no abnormality. A gastroscopic examination revealed a red and swollen mucosa.

On September 13, 1939, an erythematous eruption was observed on the face and in the groin. There was also maceration of the scrotum and the thighs. At this time 600 mg. of nicotinic acid daily dilute



PLATE III

Case 4.—Before treatment with polyvitamin. Note cheilosis lesion in angle of the mouth.



PLATE IV

Case 4.—After treatment with polyvitamin.

She was given 2 c c of polyansyn daily At the end of five days the mouth was entirely healed and the tongue was less red and painful She continued well with 10 c c of polyansyn weekly until one week before her menses when the angles of her mouth once more became sore and cracked and her tongue became red and painful The injections were continued and after menstruation ceased, the lesions promptly disappeared

With the next menses the angles of the mouth became painful but did not crack The condition disappeared before the menses were completed and the menses became less painful during treatment When last seen, May 10, 1940, she was entirely well

CASE 5 —C F, a Chinese male, 54 years old, entered the Cook County Hospital with a moderate cardiac decompensation, due to an aortic stenosis of rheumatic origin

He showed no other significant findings, except a symmetrical dry scaling eruption on the backs of the hands, the buttocks and the thighs These lesions were diagnosed as pellagra He was treated for his cardiac condition but was kept on a vitamin poor diet for ten days At the suggestion of Dr Dunbar he was given 1 000 c c of glucose intravenously on March 20 The next day all the lesions were acutely inflamed and painful and the backs of his hands were cracked and exuded serum

He was continued on the low vitamin diet and given 2 c c of polyansyn daily Improvement was prompt, and on May 9 all evidence of scaling was gone

Discussion

With the exception of Case 5, all patients had been well treated as pellagrins and yet showed little or no improvement for long periods of time The use of an extract of the anterior lobe of the pituitary gland, as already stated, was suggested by the prompt improvement of the glossitis and diarrhea in Cases 1 and 2 These cases were considered as probably pituitary cachexias The other cases had no evidence of pituitary hypofunction and yet improved with the administration of polyansyn The lesions improved by the use of polyansyn are the same as those accepted as being due to deficiency of nicotinic acid and riboflavin There is some evidence that starvation or vitamin B deficiency may lead to damage of the anterior lobe of the pituitary gland

Marburg and Wenckebach observed necrotic areas in the anterior lobe of the pituitary glands of patients dying from beri beri

Burke and McIntyre[3] found that rats on a thiamin deficient diet did not lose weight as rapidly when given a growth

promoting extract of the pituitary as did those which did not receive the extract, they concluded that the growth promoting hormone modifies the utilization of thiamin

Brenneman[4] found that when day old chicks were fed a standard diet only on alternate days growth was retarded to about 50 per cent of that of normal controls fed the same diet every day The testes were lighter in the starved chicks Male hormone limited the growth of the testes of the control chicks but not of the starved chicks This observation is interpreted as evidence of decreased production of the gonadotropic hormone This is further suggested by the fact that injection of an extract of the anterior lobe of the pituitary gland produces greater growth of the testes and combs in the starved chicks than in normal controls

Sommer[5] found that women who had passed through puberty during the starvation caused by the blockade of Germany during 1914 to 1918 showed a high incidence of abortions and still births Delayed menstruation, amenorrhea infantilism and sterility were common Corpus luteum hormones failed to cause improvement Prolan benefited many cases Greatly diminished lactation was common and was greatly improved by the use of lactogenic hormone From these observations he concluded that the lactogenic and gonadotropic hormones of the pituitary gland were diminished by starvation

Hundhausen[6] found that deprivation of vitamin B_1 caused a decrease in the thyrotropic and gonadotropic hormones in rats

From this experimental work it appears that vitamin deficiency or partial starvation may cause a decrease of the hormones of the anterior lobe of the pituitary This may serve to explain the results in all cases except Case 5 In this case, recovery occurred with the administration of polyansyn, although a low vitamin diet was continued An attempt to answer some of these questions is now being done through a series of laboratory observations

Conclusion

Evidence is presented indicating that an extract of the anterior lobe of the pituitary gland will cause recovery of pellagra lesions when they have failed to respond to nicotinic acid riboflavin, parenteral liver, and adequate diet

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SECTION V

SYMPTOMATOLOGY, DIAGNOSIS AND PROGNOSIS

CHAPTER XVIII

THE SYMPTOMS OF PELLAGRA

Definition.—Pellagra is a disease entity characterized pathologically by an erythematous, pigmented, and exfoliative dermatitis, stomatitis, glossitis, gastroenteritis, hepatitis, proctitis, urethritis and vaginitis, and clinically, by the subjective symptom syndrome consisting of burning ("scalded") sensation in the mouth and tongue, anorexia, diarrhea, burning in anal region and in the urethra, or vagina, varied nervous manifestations, emaciation, cachexia and varying degrees of anemia from the mild secondary type to the blood picture of severe primary anemia.

The classical triad of symptoms, i.e., "dermatitis, diarrhea and depression," are associated in the typical cases of pellagra, but the subclinical types, also denominated *pellagra sine pellagra*, "parapellagra," "masked pellagra," "pellagra suspect," "incipient pellagra," "latent," "dormant," or "potential" pellagra exist in which there are no skin lesions. The disease may be suspected without skin lesions in pellagrous regions by the alimentary tract symptoms, particularly unexplained sore mouth and a fiery red tongue, with, or without, diarrhea, associated with the anxiety neuroses, or in the severe cases with actual insanity. The term pseudopellagra, formerly used to designate pellagra in alcoholics, should be abandoned, or confined to cases resembling pellagra, with or without, pellagra phobia, but in which the diagnosis of pellagra can be excluded.

Classification.—Pellagra may be classified into three main groups: endemic, secondary, and alcoholic. Sporadic cases occur, but where alcohol can be excluded as a factor, they are secondary to other diseases or they are of endemic origin.

Endemic pellagra, and to a less extent alcoholic and secondary pellagra, may be classified as acute, subacute, and chronic, and according to severity into four types

1 The mild type in which the symptoms are referable largely to the alimentary tract associated with psychasthenia, especially the anxiety neuroses, and mild dermatoses This type tends to recovery, if properly treated, and in many cases the symptoms of pellagra subside without treatment

2 The moderately severe type which tends to chronicity, with recrudescences of symptoms year after year

3 *The* severe type in which the oral, gastrointestinal, skin, and nervous symptoms exist to a marked degree, and which tends to progress to fatal termination Alcoholic pellagra often belongs to this type

4 The typhoid type is seen most frequently in localities in which pellagra is endemic In the typhoid type the onset is more or less sudden, the diarrhea is intractable, the mouth symptoms are severe, the skin lesions are of the bullous or wet type with secondary pyogenic infection there is high fever, rapid pulse, prostration, rapid emaciation and death in a high percentage of cases Fortunately the typhoid type is now rare It was observed frequently when pellagra was first found to be endemic in the United States

Pellagra also may be classified as primary, in the endemic form, or it may be secondary to, and not infrequently the terminal stage of, chronic conditions and diseases such as alcohol addiction, carcinoma of the esophagus and stomach, ulcerative colitis, and other severe chronic gastrointestinal diseases in which nutrition is impaired

Subclinical Pellagra—Pellagra in the early stages responds readily to treatment except in the acute fulminating cases seen in severe outbreaks It therefore is important to make an early diagnosis of pellagra at a time when the symptoms result from physiologic dysfunction before irreparable pathologic changes have taken place The physician who waits until the erythematous eruption appears on the dorsal surfaces of the hands, arms, neck, and feet before making a tentative diagnosis of pellagra

in a person residing in a pellagrous community, or in an alcoholic, may miss the opportunity of curing his patient

It is not easy in every case to make a diagnosis of pellagra before the eruption appears, but given a patient who resides in a community in which pellagra is endemic, there are certain symptoms from which the physician experienced in dealing with pellagrins may make a tentative diagnosis of "subclinical pellagra," formerly and perhaps more expressively called *pellagra sine pellagra* It is wiser to treat a hundred patients with suspected pellagra as if a positive diagnosis had been made, than to allow one patient to go untreated while waiting for the dermatitis, diarrhea, and mental depression to appear

Alimentary tract disturbances and nervous and mental manifestations usually precede the dermatoses in pellagra though occasional cases occur in which there are skin lesions before the patient complains of a burning or scalding sensation in the mouth, loss of appetite, decrease in weight, vague abdominal discomfort, associated with general apathy, the anxiety neuroses and varied paresthesias

The Pellagra Facies—The pellagra facies is difficult to describe, but it often exists before any one of the overworked triad of symptoms, i e, "dermatitis, diarrhea, and depression,' appear Charles Wardell Stiles, a great sanitarian, retired surgeon of the United States Public Health Service, used to make the diagnosis of uncinariasis by the "dull, fishy stare" of hookworm victims He would inspect a group of children in hookworm districts and point out the victims of uncinariasis and his diagnosis would be confirmed by finding the ova of uncinaria, or larvae, or the adult hookworm, in the feces of those whom he had pronounced as having the "lazy disease" Physicians who have had a large experience in treating ambulatory cases of pellagra can make a "snap shot" diagnosis in many cases before the patient has described his symptoms

The appearance of the eyes of pellagrins may not be distinctive, but usually the pupils are dilated, the sclera is not clear, but bluish, the color of lead, the eyes and eyelids move slowly, and there is a characteristic dull lifeless stare There is an anxious or querulous expression on the face of the pellagrin, who seems to realize that something is wrong with him,

he does not know what, but he has come to the doctor to find out Frequently it is evident that he is afraid he has pellagra, and appears distinctly anxious because he fears he will be told he has the dreaded disease, of which some of his neighbors have died, or have 'gone crazy,' and of which he has read so much in the papers Wilson in discussing the pellagra facies said "The patient has a characteristic anxious expression around the eyes, which is so marked that a diagnosis can often be made by this symptom when others are indefinite"

The ambulatory pellagrin seeking treatment may appear more anemic than the laboratory blood findings indicate He has a "muddy" complexion and not infrequently there is slight pigmentation or macular eruption over the face particularly over the alae of the nose, and on the exposed surfaces of the neck, before there is dermatitis of the dorsal surfaces of the hands

Early Mouth Symptoms—One would hesitate to make the diagnosis of subclinical pellagra from the complaint of burning in the mouth with reddened mucosa of the oral cavity and a red tongue, especially around the edges and at the tip Sore mouth occurs in many conditions not related to pellagra Perhaps the most frequent condition that causes painful stomatitis is a simple anachlorhydria, which clears up promptly by the use of teaspoonful doses of dilute hydrochloric acid given in milk with meals and three hours after meals but given in alcoholic or a patient residing in a pellagrous district, who complains of burning in his mouth whether he has demonstrable stomatitis or not he should be regarded as a potential pellagrin, if not an actual case of pellagra Spies and Blankenhorn have been impressed with the importance of early mouth lesions in their experimental and clinical studies of pellagra

Early Gastrointestinal Symptoms—The wise physician will suspect pellagra when he is called upon to treat a chronically ill individual, in a locality in which there are known cases of pellagra, where the patient complains of loss of appetite, vague abdominal symptoms, such as "gas on the stomach" with or without gaseous eructations, epigastric distress, either burning and indescribable discomfort, or colicky pains The potential pellagrin will complain also of what he may call "acute indigestion" which he believes was brought on by eating various kinds

of food and often he will deprive himself of needed nutritious food because he fears that it will bring on another attack

Constipation is present in at least three fourths of the cases of subclinical pellagra A mild diarrhea, however, may appear concomitantly with mouth symptoms Diarrhea alternates with constipation long before chronic diarrhea supervenes

Early Nervous Symptoms—The lamented J W Babcock, of South Carolina, one of the great pioneers in the study of pellagra, and Marvin L Graves, an illustrious Texas clinician in their early studies of pellagra stressed neurasthenia, of which the anxiety neuroses are a part, as the most important early manifestation of pellagra Babcock found in studying the several hundred patients with pellagra whom he had treated, that a large proportion of them had been classed and had been treated as "neurathenics" or "neurotics" for years before the typical symptoms of pellagra developed Babcock considered neurasthenia, a term which he did not like but used for lack of a more descriptive name, as the one most important predisposing cause of pellagra, so much so that he regarded any nervous individual who lives in a pellagrous locality as a potential pellagrin, who should be treated as if he were known to have the disease Babcock believed that many cases of pellagra may be prevented if physicians will correct the hygienic environment and build up the nutrition of nervous patients, paying particular attention to the diet and the mental hygiene of the individual and his family

Longmire, of Texas, who has had a large experience in dealing with pellagra, believes that the diagnosis can be made, or at least suspected, for months or years before the dermatitis and diarrhea become pronounced He thinks that the nervous individual in a locality in which pellagra is known to exist, whose symptoms cannot be ascribed to known causes, should be diagnosed as a pellagra "suspect" and treated accordingly Longmire regards insomnia with varying degrees of mental perturbation, particularly worry as a frequent complaint of pellagrins He says that "some are irritable, some are depressed and others exhilarated, and these are often classified as cases of nervous breakdown or nervous exhaustion," particularly in the spring and summer, with a history of improvement during the winter

J B McLester, in studying the case histories of a large number of pellagrins in Hillman Hospital in Birmingham, was impressed with the proportion of patients who gave histories of digestive symptoms for years before skin lesions appeared

The subclinical type of pellagrin, before a definite diagnosis can be made, often complains of burning of the hands and feet, without any evidence of skin lesion Sometimes there are paresthesias not referable to the distribution to the various nerves in which the neuritides may occur Anesthesia of the skin in pellagra is rare, but pellagrins often complain of numbness and tingling of the hands and feet, and of what they may call "a dead feeling all over"

Finally, it should not be forgotten that pellagrins may become psychotic before typical symptoms appear

In making a tentative diagnosis of subclinical pellagra it should be remembered that mild skin lesions, particularly a recurring erythema on the backs of the hands, appearing in the spring and summer, may be observed for years before there are alimentary tract symptoms

The term pseudopellagra formerly used to describe pellagra in alcoholics should be abandoned A person either has, or has not, pellagra, and pseudonyms like pellagroid and parapellagra certainly have no place in the nomenclature of the disease

The Anamnesis—Careful history taking is important if one would make the diagnosis of subclinical pellagra In history taking the patient's complaints in his own words should be recorded The physician who is in a hurry and who does not give his patient time to tell the story of his illness in his own way is not a careful diagnostician, because the anamnesis is the most important single item of the data from which a diagnosis of subclinical pellagra can be made It is admitted that the patient's history of his illness is misleading at times, but the physician should learn to evaluate this patient's statements along with the information he derives from physical examination and laboratory studies

Thompson Frazer, in reporting a series of cases which he studied with regard to the first symptoms, stressed the importance of the anamnesis He said that if careful histories be

taken, it will be found that a surprisingly large number of pellagrins have symptoms months, and in some instances years, before the advent of the symptoms which prompted them to consult a physician

Incubation Period—The period of incubation in pellagra has been discussed by a number of writers, but no one has given any definite period of time for the development of the disease One of the arguments against the infectiousness of pellagra is that no one has been able to point out a period of incubation from the time of exposure to the supposed infection to the time that the disease appears Siler, MacNeal and Garrison in their studies of a large number of cases in the cotton mills in the suburbs of Spartanburg and other endemic foci in that part of South Carolina, estimated that it required about a year's residence in a pellagrous district before a victim manifested symptoms of pellagra

Early Skin Lesions—Menage has called attention to dermatoses as being in many cases an early manifestation of pellagra He said

> "The skin eruption of pellagra is not always a late or terminal manifestation but may be a very early one
>
> "We should be willing to make a diagnosis of pellagra on the skin lesions, without the symptom complex because if an early diagnosis is made, therapeutic measures may be instituted and thereby save the patient the burden of proving his own diagnosis which he surely will do if left untreated "

Bass reported cases in which the bilateral erythema on the backs of the hands had recurred for a number of summers before other symptoms of pellagra appeared

Oral Manifestations—At varying intervals before the skin lesions appear, the pellagrin may complain of a "scalded feeling" in the mouth, which he may ascribe to drinking hot coffee This may last only a few weeks, during an exacerbation with other symptoms, or it may continue for months or years Sometimes the pellagrin complains of actual pain in the mouth, particularly of the tongue, which may be so severe that he refuses to eat The pain may be increased by eating coarse foods or taking hot or cold drinks Acids may increase the burning in the mouth The fiery red tongue is frequently sore, the gums

are tender and bleed easily. Salivation is profuse at times, the saliva dribbling continuously from the mouth. Increase in the flow of saliva may be complained of when there are few other symptoms.

In the very early cases when the mouth is examined there may be no evidences of a stomatitis, the tongue, gums, and the buccal surfaces appearing normal, yet the pellagrin's mind is focused on his mouth symptoms, and he believes that he can never get well. The tongue, in some cases, is dark red in color, and fissured, resembling rare beef. There may be aphthous patches and even deep-seated ulcerations on the edges and underneath the tongue. The buccal mucous membranes are very much reddened, particularly around the edges of the lips. Sometimes the outer edges of the lips appear inflamed and red before the mouth is opened. The gums also are reddened, and, in some cases, spongy and ulcerated, somewhat as in mercurial stomatitis. As the disease progresses the glossal epithelium is shed and the tongue appears red and glazed, particularly at the end and on the margins. The buccal surfaces of the cheeks, the hard and soft palates, and the fauces appear reddened. In the severe cases, painful ulcers on the tongue, the gums, the frenum, and buccal surfaces appear. Pyorrhea alveolaris may be severe, and in advanced cases, there is dirty and foul oral sepsis, resembling severe Vincent's angina. In many cases the Vincent's spirillum is present, and often streptococci and staphylococci are secondary invaders.

Esophagus.—The burning sensation in the mouth may extend to the esophagus, and substernal pain is sometimes pronounced. Roussel called attention to dryness of the esophagus, with dysphagia, as *one of the early symptoms*. I have noted it in several cases, and regard it as an important symptom. Globus hystericus may be present in pellagra patients with other nervous manifestations.

Gastric Symptoms.—Symptoms referable to the stomach may be among the *first manifestations of pellagra*. Loss of appetite is one of the earliest and most constant complaints of the pellagrin. A feeling of satiety after eating small quantities of food (acoria) is complained of, and frequently when there is discomfort after eating, sitophobia may exist.

Later, the burning pain over the epigastrium, pyrosis, and sometimes over other parts of the abdomen appears as the most disagreeable, persistent, and characteristic symptom referable to the stomach The burning sensation in the abdomen, of which pellagrins of all stages complain, is very different from that seen in peptic ulcer In pellagra the burning sensation is constant day and night, and it is not relieved, but is accentuated often, by eating

Distention of the stomach or a feeling of fullness in the epigastrium after eating is often a distressing symptom Gaseous eructations usually due to aerophagia nervosa, are common The pellagrin usually shows the doctor how much gas he has on his stomach, and he will be observed to swallow air before beginning noisy eructations There may be gaseous distention of the abdomen and tenderness over the epigastrium, in some cases over the entire abdomen, but often when the diarrhea is severe, the abdomen may be flattened

Nausea is common and an early symptom The nausea is more or less constant often appearing before breakfast and lasting throughout the day until bedtime, and not infrequently the pellagrin is nauseated at night Eating increases the nausea, but vomiting usually does not appear until late in the disease, when it may be a distressing symptom Occasionally attacks of vomiting may occur, fairly early, which the victim often believes is due to some article, or articles, of food which he names as the cause of the attacks Not infrequently pellagrins will discard meat eggs, milk, bread, and other articles of food because they have disagreed with them in attacks of what they call "acute indigestion" In the late stages of pellagra, nausea and vomiting may be severe and small amounts of blood may be vomited

Vague abdominal discomfort is often an early complaint in pellagra It is sometimes intensified after meals, but more often is not related to eating Cramping abdominal pains may be present, simulating gall bladder colic, or what is called chronic appendicitis, or even peptic ulcer Not a few pellagrins carry abdominal scars and continue to have the pains, or the discomfort, for which an unnecessary operation had been performed

Intestinal Manifestations—Constipation, associated with what the pellagrin calls "biliousness" is an early manifestation

of pellagra Not infrequently recurring attacks of mild diarrhea alternating with constipation are complained of for months or years before the diarrhea becomes severe and constant Colicky pains associated with constipation and the passage of mucus after purgation are early manifestations Mucous colitis, with constipation, or diarrhea, occurs more frequently in patients in whom constipation alternates with, or is followed by, diarrhea

The stools of pellagrins are not characteristic until diarrhea has been established, when they are small, frequent, and watery The diarrhea varies from looseness of the bowels two or three stools per day, to 20 or 30 bowel movements within twenty four hours In some cases, the diarrhea is of a dysenteric character, 4 or 5 stools per day, containing mucus and blood and preceded by griping pains In the severe cases, there is a profuse liquid diarrhea that oftentimes weakens a patient very rapidly, and frequently is followed by death In one of my malignant cases of pellagra, a large hemorrhage from the bowels was the exciting cause of the patient's death

The stools may, or may not, be preceded by griping and the bowel movement may or may not, relieve the abdominal discomfort Sometimes pellagrins complain of weakness and an "all gone" feeling in the abdomen after bowel movements

Abdominal tenderness may, or may not, be present in pellagra in the early stages, but in the late stages when there is diarrhea, there generally is pronounced tenderness over the abdomen, particularly in the lower right and left quadrants In the less severe cases, there may be localized tenderness, particularly in the upper right quadrant The pain under the margins of the ribs on the right may be due to hepatitis, more than to gall bladder pathology because autopsies show involvement of the liver in 95 per cent of the fatal cases of pellagra Turner and others have reported pellagra in which gall bladder disease preceded and seemed to have been an etiologic factor of the disease

Rectum—A constant desire to evacuate the bowels because of burning or rectal irritation may become an annoying complaint The burning pain in the rectum, either with or without diarrhea, is one of the most constant complaints of pellagrins Examination of the anal region shows redness, and proc

toscopic examination may reveal a diffuse redness of the rectal mucosa, and sometimes ulcerations in the rectum

Emaciation and Cachexia—Some loss of weight is the rule in pellagra though many observers have reported pellagra in well nourished individuals and even in overweight patients For instance, in Busman's 27 patients "eleven gave no history of an abnormal or deficient dietary intake Only five were definitely emaciated as the result of chronic malnutrition "

In the mild cases and in the early stages of any case of pellagra, there may be a loss of only a few pounds of weight, but as the disease progresses, particularly when there is severe diarrhea, the emaciation may be extreme There is no more pitiful sight than a pellagrin in the last stages of the disease

Dehydration is pronounced in the patients with severe diarrhea, the skin of the entire body becomes dry and wrinkled Often the victim of pellagra becomes cachectic with much the appearance of the starved cancer victim

Nervous Symptoms—The nervous symptoms of pellagra, while often bizarre, present a more or less constant syndrome In the early stages the pellagrin complains of weakness and a feeling of general discomfort He recognizes that he is not so alert mentally as he has been his memory is impaired, and he is anxious lest he is losing his mind or fears that he will become seriously ill He may have various abnormal fears, and pellagra has been so widely propagandized that pellagraphobia often is his most distressing complaint It may be added that physicians see a great many more patients particularly in regions in which pellagra is endemic, who have pellagraphobia, and not pellagra, than they see of true pellagrins

Fatigue—The fatigue syndrome in which the patient complains of tiring easily, and says he has no energy and feels unable to do his work satisfactorily often appears before there are digestive or nervous symptoms Slight mental confusion in which the patient cannot concentrate his mind on his work, or when reading or playing, is an early symptom becoming more pronounced as the disease progresses In such cases the blood pressure usually is low (80 to 95 systolic and 60 to 80 diastolic), suggesting that hypoadrenalinism may be a factor in pellagra

Insomnia.—Insomnia is a more or less constant nervous manifestation of pellagra. The pellagrin usually cannot explain why he cannot sleep, but sleeplessness is frequently associated with various paresthesias and other functional nervous symptoms. The pellagrin not infrequently magnifies the depression that comes from loss of sleep and believes that is one of the reasons why he is "going crazy."

Headaches are not constant in pellagra, but in the early stages, in particular, the pellagra patient may complain of a dull aching in the top of his head. Vertigo is another common complaint of pellagrins, a condition which in the country districts they usually ascribe to "biliousness." Tinnitus aurium, or "roaring in the head," is sometimes annoying.

Mental Depression.—Mental depression sometimes to the degree of melancholia with suicidal tendencies, and other types of depressive psychoses are perhaps the most important and most constant neurologic manifestations of the late stages of pellagra. If the diagnosis of pellagra is made early, fewer pellagrins will become psychotic. The proportion of pellagrins which a physician sees outside of an insane hospital depends much on his ability to make an early diagnosis of pellagra, and also upon the financial ability of the pellagrin to carry out the proper diet and medical treatment, thus preventing the psychoses.

Sensory Disturbances.—Sensory nervous disturbances appear early in pellagra. They are protean, and often ill defined, but careful questioning may reveal that the pellagrin had a burning sensation in his hands and feet long before there were any evidences of any skin lesions. Formication, or a feeling as if insects, ants in particular, are crawling over the body, is a frequent complaint of pellagra patients from rural communities. Cramps of all kinds, abdominal cramps, cramps in the calves of the legs and in the arms are frequent subjective symptoms.

Sometimes the pellagrin complains of constant or transient pains in various parts of the body, more particularly in the back. The back pains are often exaggerated on rising out of bed or when sitting or walking. The pains may radiate to the hips and down the legs.

Motor Symptoms.—Muscular weakness is a primary symptom of pellagra and the myasthenia advances as the disease progresses. Pellagrins often complain of stiffness of the muscles and joints. Muscular atrophy is pronounced in the neglected severe cases.

Tremors and fibrillar twitchings also are seen often in the early stages of even the mild cases, and they are almost always present in the severe cases. There may be coarse tremors of the hands and fine tremors of the tongue.

The gait of the pellagrin is normal except in about 10 per cent of the cases when cord changes occur, causing ataxia and other evidences of posterior root involvement or multiple sclerosis. The knee jerks are usually exaggerated. Tucker reported in a study of 74 cases that the knee jerks were exaggerated in 62 per cent, decreased in 9 per cent, and absent in 10 per cent. He also reported that ankle clonus, the Babinski, and other pyramidal tract signs are rare.

As a rule motor symptoms occur late in pellagra, though general muscular weakness, particularly of the lower limbs, is an early complaint of pellagrins. Undoubtedly permanent cord changes occur in pellagra, as they do in pernicious anemia, though less frequently. It is an interesting fact that autopsy studies on pellagrins and pernicious anemia victims show similarity in cerebral, cord, and posterior nerve root pathology when they exist. It appears more than a coincidence that in the treatment of pellagra and pernicious anemia when cord lesion symptoms are present the characteristic symptoms of each disappear, but the symptoms referable to cord and spinal root changes persist after the other symptoms have been relieved.

Recovered Case With Permanent Cord Changes.—I recently had the pleasure of treating a lovely, intellectual, and prosperous woman, 78 years of age, whom I had treated and cured of pellagra in 1914. She had been symptomless, except for ataxia, and had consulted a physician but once (and then for a minor complaint) in twenty-four years, when, in 1938, she came to the hospital for treatment of advanced cardiovascular disease. Her case history made in 1914 was found. Her complaints at that time were as follows: "Annual spring and summer recurrences of dermatitis, diarrhea, and mental depression for 4 or 5 years."

before she came to Mobile for treatment She also complained of "weakness and staggering gait" She remained in the hospital for four weeks and on a high caloric, rich vitamin diet and was given symptomatic medical treatment All her symptoms disappeared, except those referable to the irreparable damage to the spinal cord and posterior nerve roots Weakness of her lower limbs, staggering gait, and partial loss of her sense of balance, symptoms that she had when she had pellagra, persisted Her patellar reflexes were markedly exaggerated She remembered having been told before leaving the hospital in 1914 that she could hope for a complete cure of the pellagra, but that she would have the staggering gait and muscular weakness of her lower limbs for the remainder of her life Throughout twenty four years of excellent health, she has had to be careful in walking, or she would lose her balance and fall She now presents a typical picture of advanced arteriosclerotic myocardial disease Her blood pressure ranges around 220 systolic and 120 diastolic, and her electrocardiogram shows left ventricular preponderance with evidence of coronary sclerosis

✓**Boggs and Padget's Analysis** —Boggs and Padget's analysis of their 102 cases showed a high percentage of symptoms referable to spinal cord pathology They found 46 cases (45 per cent) with involvement of the spinal cord, which they said is in general like the subacute combined sclerosis of pernicious anemia, though showing more tendency to implicate the posterior columns The degree of involvement varied from diminution, or loss, of the knee jerks with subjective numbness and tingling, to severe combined sclerosis, amounting to paraparesis or paraplegia with ataxia, paresthesias and partial anesthesia Boggs and Padget state that sphincter weakness or paralysis may occur in such cases There was little variation in the incidence for the three groups In all groups and equally true for each, the mortality rate was much higher in the cases manifesting cord changes than in those which did not

Boggs and Padget's cases were largely senile derelicts in the Baltimore City almshouse, which may account for the high incidence of cord symptoms in their series of cases of pellagra

✓**Mental Symptoms** —W D Partlow, Superintendent of the Alabama Insane Hospitals, who has had as large an experience

with pellagra as any man in the United States, asserts that an actual psychosis, sometimes of a severe type, is often the first manifestation of pellagra He states that he and his associates often predict with more or less accuracy, when such patients are admitted to the psychopathic wards of the Alabama State Insane Hospitals, that they later will develop alimentary tract symptoms and the dermatoses of pellagra

Pound, of the Florida State Insane Hospital, in discussing the neurologic manifestations of psychotic pellagrins, said that the psychoses of pellagra may simulate any type of mental disease, only one feature of which may be regarded as distinctive and that is the depressive character The mental symptoms may vary from mild melancholia to mania The functional nervous symptoms appear early Several weeks or months before the appearance of other symptoms there is a complaint of progressive weakness and loss of energy, "rundown condition," coming on and growing worse during the late winter or spring months

E D Bondurant, of Mobile, a neuropsychiatrist, who has had a large experience in treating pellagra, in summarizing the nervous phenomena of the disease said that the earliest and most constant symptoms of damage to the nervous organs are such as are usually grouped under the term "neurasthenia" "In practically all cases in which any semblance of history can be obtained, we find that along with the initial ill health and sometimes preceding it there has been nervousness irritability, moodiness, fatigue, lowering in intellectual capacity introspection, hypochondria, etc "

In discussing the motor symptoms of pellagra, Bondurant said that muscular weakness with tremor and fibrillar twitching, is noted in almost all cases, especially conspicuous in the later stages of the unfavorable rapidly fatal ones, in which speech defects, slurring and indistinctness of articulation are prominent

The tendon reflexes as a rule are exaggerated ankle clonus, spastic rigidity, and spastic gait occur in the late stages of many of the fatal cases

Buchanan, formerly psychiatrist of the East Mississippi Insane Hospital at Meridian said that he did not understand the

term pellagrous insanity, because the mental symptoms in pellagra are not different from those observed in other patients. Practically the same conditions in those who become insane from ill health and general debility due to other diseases are seen in pellagra. Some of the late nervous manifestations of pellagra so closely resemble the symptoms found in degenerative nervous diseases, such as syphilis and paresis, that it would be difficult to make a diagnosis from the nervous and mental symptoms alone, but taken in conjunction with the other symptoms of pellagra, the diagnosis is easy.

Boggs and Padget, in discussing the mental symptoms found in their series of 102 cases in the Baltimore City Hospital, said that 51 patients, or 50 per cent, showed some type of psychosis, but of these, in only 26 (25.5 per cent) were the psychoses thought to be pellagrous in their origin. Eleven of the remaining 25 had been under observation in the Psychopathic Hospital for periods varying from one to five years, and had developed pellagra as a complication of the mental disease. The other 14 had typical alcoholic psychoses, such as delirium tremens, or Korsakoff's syndrome. They regarded the psychosis of pellagra as being of the acute hallucinatory type at the onset, and later the patients develop paranoid trends, with delusions supplanting the hallucinations. Boggs and Padget regarded insanity as of grave prognostic significance in their pellagra patients.

It should be remembered that Boggs and Padget were dealing largely with the old neglected cases. It therefore would be expected that they would have a larger proportion of cord and central nervous system changes than would be found in private practice.

CHAPTER XIX

SKIN MANIFESTATIONS OF PELLAGRA

Variable Skin Lesions.—The skin lesions of pellagra are variable in distribution and in intensity. Usually the dermatitis is preceded by alimentary tract and neurologic symptoms, though in a few cases bilateral symmetrical erythema on the backs of the hands is seen with but slight or no symptoms referable to the digestive tract or the nervous system. Bass cites a case of the late Sidney Simon who had to wear gloves when exposed to the sun for twenty nine years before he developed the digestive symptoms of pellagra. H. F. Harris cites, and agrees with, Neusser that "pellagra may occur as an essential dermatosis unaccompanied by any of the other classical symptoms of the disease."

Sunburn.—Usually the very first skin lesion is what the pellagrin calls "sunburn" on the face and backs of the hands. On inspection of the dorsal surfaces of the hands in the first stage of the dermatitis, there is a sharply defined area of very red skin, extending from the wrist joint to the first metatarsal joint. This erythema gradually increases in intensity, accompanied by thickening and discoloration of the skin over the affected area. This eruption lasts a variable length of time, from one to three weeks, when the thickened pigmented epidermis peels off leaving a whitish thin parchment like skin that persists for months or years.

Face.—Pigmentation of the face particularly over the cheek bones and nose may occur, giving the patient a negroid appearance, and at times there is a brownish pigmentation of the skin over the entire body, resembling and with much the same distribution as the characteristic epidermal discoloration seen in Addison's disease. Thannhauser suggested that, because of this pigmentation, there must be deficient secretion of the suprarenal glands in pellagra as in the Addison syndrome.

Bass reported that in 20 per cent of his cases there was a macular eruption which extended over the entire body, but was more pronounced on the abdomen, arms, and legs. The macules



Fig 37 —Showing eruption on nose cheeks around mouth, and neck Note the V shaped area over sternum and clavicles (Courtesy of *Ruffin and Smith*, Duke University School of Medicine)

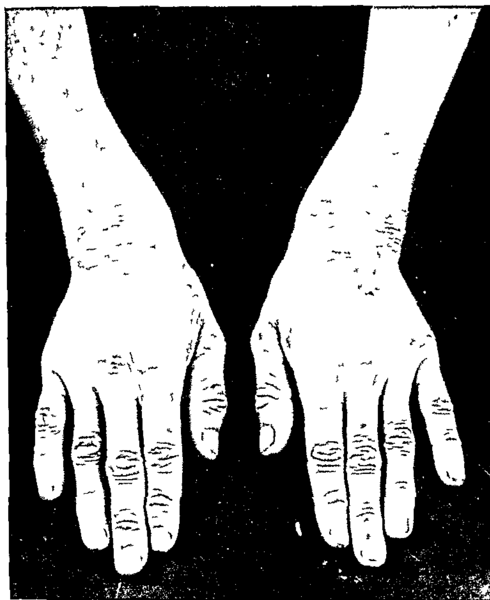


Fig 38 —Typical bilateral pigmented erythematous rash on dorsal surfaces of hands of the same patient (Courtesy of Ruffin and Smith Duke University School of Medicine)



Fig 50.—Bilateral eruption on feet of negro, showing irregular pigmentation and exfoliating areas (Courtesy of Ruffin and Smith, Duke University School of Medicine)

The Duke University group and others, who have investigated the photodynamic factor in pellagra, were able to produce unilateral skin lesions of pellagra over various parts of the body, without the characteristic desquamative erythema over the dorsal surfaces of the hands and face and other regions of the body ordinarily affected in pellagra

Vaginitis—In females, vaginitis, with reddened, raw, surfaces around the introitus, may appear early, and the burning in and around the vagina is an annoying complaint Bass in studying cases of pellagra in women and girls found that 23 gave a history of "female trouble," usually vaginitis, with discharge and pruritis Some of them thought they were disgraced by these symptoms and believed that they were under suspicion of being immoral

Groins and Scrotum—The "weeping" reddened erythematous, pigmented eruption in the groins of males, usually described by pellagrins as 'chafing," may appear early along with the lesions of the dorsal surfaces of the hands Goldberger and Wheeler regarded scrotal lesions as the most constant skin manifestation of pellagra, but this opinion is not concurred in by most physicians, who assert that scrotal lesions are rare in pellagra, and when present they are secondary to the lesions on the exposed parts of the body, particularly on the face and the dorsal surfaces of the hands H F Harris, Isadore Dyer, C C Bass, and J S McLester are among the clinicians who have had large experience in dealing with pellagra and who regard scrotal lesions as being rare in pellagra Not infrequently an irritating urethritis with watery secretion and redness of the meatus is seen in males Proctitis and inflamed areas in and around the anus are found frequently in the characteristic eruption on other parts of the body in both males and females

Dyer on Skin Lesions—The late Isadore Dyer, Professor of Dermatology Tulane Medical School stressed the difficulties in the diagnosis of pellagra from skin lesions alone He said

'From the dermatologic point of view pellagra presents not a fixed type which is always present and any attempt for a diagrammatic scheme for the diagnosis of pellagra is apt to be confusing because so many cases show skin evidences which are variable in their appear

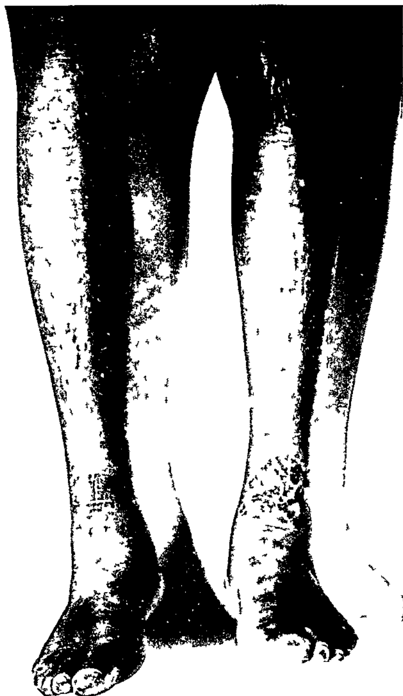


Fig 50—Bilateral eruption on feet of negro, showing irregular pigmentation and exfoliating areas (Courtesy of Ruffin and Smith Duke University School of Medicine)

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ance Among the cases which I have seen only two have presented a pure erythema at all, and in these the erythema was associated with some exudative or alternative change in the skin The process may be even eczematoid

"If there is any one point which stands out as characteristic in the variant eruptions, it is the tendency to keratosis Wherever the pellagra eruption persists for any time, a smaller or greater part of the eruption becomes keratinized, usually with spirous points about the hair follicles"

Dyer concluded that "one should be slow to make a diagnosis of pellagra on the skin symptoms alone, as, even in well established cases of pellagra, the local evidences may be far from classic, and may actually be only an erythema multiforme brought on by intestinal conditions"

Rutledge on Pellagra Dermatoses—Winston U Rutledge, a dermatologist of Louisville, Kentucky, in describing the skin lesions that occurred in four cases of alcoholic pellagra, shows the variability of the dermatoses in that type of the disease It may be added that the skin lesions of pellagra in alcoholics do not differ from those found in the endemic type of the disease For the reason that Rutledge's description of the skin lesions of pellagra is one of the best that has appeared in medical literature it is reproduced in this chapter Rutledge said

"The erythema pigmentation and vesiculation progressed until the entire dorsum of both hands and fingers, down to the terminal phalanges were involved The hands became swollen and tender and the patient suffered from a burning sensation in them The blisters spread until the backs of both his hands were covered with large confluent bullae which later broke leaving the denuded areas crusted dry, fissured and very painful but under applications of vaseline, the skin slowly softened and healed to a large degree Four weeks after the onset of this condition the patient felt much better and on the invitation of a friend he drank a half pint of 'Blue Heaven' an alcoholic concoction of the most inferior variety That same night his hands began to burn severely and the following day the backs of both hands were again intensely red and painful

"This stage was again followed by vesiculation desquamation and crusting He drank no more from this time until coming to the clinic On admission, he presented a sharply delimited symmetrical eruption on the dorsum of both hands and proximal phalanges The skin over the involved portion of the fingers showed only a moderate erythema and pigmentation while extending from there over the backs of both hands to a line about one inch above the wrists the skin was in some places intact and of a brownish red color, while other portions were raw and painful from the rupture and desquamation of the large

bullae Around their margins were tags of shriveled epidermis and a few small vesicles filled with sero purulent fluid There was no involvement of the palms or flexor surfaces of the wrists

' The three other cases were likewise seen in the early stages of the disease when their chief complaints centered about the condition of their hands which were swollen and painful and showed symmetrical glove like involvement of the skin on the backs of them and also the proximal and middle phalanges Over these parts the skin presented varying degrees of erythema, pigmentation vesiculation crusting and scaling

"In two cases the dermatitis stopped abruptly at a line drawn just above the wrists while in the third there was a blotch purplish red, purpuric discoloration of the skin on the dorsum of the forearms which extended to just above the elbows This latter involvement had developed in spite of the patient denying any direct exposure of his forearms to sunlight "

CHAPTER XX

COMPLICATIONS

The skin lesions, the gastrointestinal symptoms, and the neurologic manifestations, including the dementia, of pellagra are all a part of its syndrome, and none of them can be considered as complications. It also is evident that the severe degrees of macrocytic anemia sometimes seen in pellagra result from the same etiologic factor, or factors, responsible for the other manifestations of the disease and anemia cannot be regarded as a complication of pellagra.

There are no characteristic complications in pellagra. The pellagrin also may have other diseases, just as patients who have pernicious anemia, sprue, tuberculosis, and syphilis may have coincidental maladies which may, or may not, affect the course of the disease. The pellagra patient, if he is not treated promptly, or if he does not recover spontaneously, as he grows progressively weaker and therefore becomes less resistant to all infections, may develop terminal diseases, particularly the infections of the respiratory tract. Pneumonia which Osler called "the old man's best friend," is the disease which most frequently relieves the "misery" of the hopelessly ill pellagrin. The pellagrin may have latent tuberculosis, which becomes active and thus a complicating factor, and even the cause of death in not an inconsiderable proportion of cases. Syphilis is frequently associated with pellagra, and its severity is perhaps increased because the pellagrin presents a fertile field for propagating the *Treponema pallidum*. Apparently the death rate of pellagrins who have syphilis is higher than of nonsyphilitic individuals who have pellagra.

In our experience intestinal infestations with the *Endamoeba histolytica*, cercomonads, trichomonads, and other protozoa are not infrequent. Jelks, of Memphis, has found protozoan infestations so frequent in his cases of pellagra that he regards them as possible etiologic factors. On the other hand Syden

stricker and Armstrong in studying 440 cases, and there can be no doubt of the thoroughness of their studies, found amebiasis in only 3 cases Ellinger, Hassan and Taha in recent investigations of pellagra in Egypt found "intestinal parasites almost invariably present in pellagrins and much less frequent in the nonpellagrous population "

Heart complications occur in pellagra but they are relatively infrequent while in beriberi known to be due to avitaminosis (deficiency of vitamin B_1), the heart is almost invariably involved in the severe cases Heart complications cause death infrequently in pellagrins, while in beriberi, heart disease is responsible for most of the fatal cases

Urinary tract infections occur in pellagra, but as a rule they are not serious complications The female pellagrin may have, or develop, pelvic infections, perhaps not more frequently than do nonpellagrous women

The eruption in pellagra may become pustular from secondary infection and in some cases ulceration of the affected areas, particularly in the hands and feet, may occur Septicemia may occur in such cases Pellagrins are prone to develop bed sores

TABLE XV

DISEASE	NUMBER OF PATIENTS	PATIENTS RECOVERED	FATAL CASES
Amebiasis	3	3	0
Arteriosclerosis	10	8	2
Arthritis	2	1	1
Asthma	3	3	0
Bronchopneumonia	25	2	23
Cerebral hemorrhage	2	1	1
Granuloma venereum	2	2	0
Heart disease (all types)	30	22	8
Helminthiasis	5	5	0
Hypertension (essential)	7	5	2
Hyperthyroidism	1	1	0
Malaria	4	4	0
Meningitis (septic)	1	0	1
Morphinism	2	2	0
Nephritis (all types)	4	1	3
Obesity	1	1	0
Otitis media acute	1	0	1
Pelvic inflammation	14	11	3
Pneumonia, lobar	2	0	2
Pulmonary abscess	1	0	1
Starvation	4	0	4
Syphilis (all stages)	57	42	15
Tuberculosis	18	12	6
Urinary infections	13	13	0

because of emaciation and lack of cleanliness With careful hospital management decubitus ulcers rarely occur

Sydenstricker and Armstrong in reviewing 440 cases of pellagra found that more than 50 per cent had complications, thus proving that pellagrins are prone to many diseases Table XV shows the 215 varied complications they found in studying the 440 cases

CHAPTER XXI

LABORATORY FINDINGS

Anemia.—In the majority of cases anemia is not pronounced in the early stages Often the pellagrin appears anemic when his red blood count may be normal As the disease progresses, slight anemia appears and even in severe and fatal cases there may be only moderate degrees of anemia In other words the degree of anemia in pellagra is not always in proportion to the severity of the disease Certainly the blood picture in pellagra is neither characteristic nor constant

The anemia of pellagra is of the secondary type, except in a small proportion of cases, when the blood picture cannot be differentiated from pernicious anemia Several cases of pernicious anemia have been reported as having been associated with pellagra, and a number of cases have been followed by severe macrocytic anemia after recovery from pellagra

Turner s study of the blood in 50 cases of pellagra concurs with the findings of most clinicians He found that 56 per cent showed no appreciable anemia, in 12 per cent there were moderate degrees of anemia in 12 per cent the anemia was pronounced, and in 4 per cent the red blood counts were extremely low

Spies and Chinn found a high percentage of mild secondary anemia among alcoholic pellagrins, 19 of their 30 patients had an average red cell count of 3,500,000 and an average hemoglobin of 74 per cent Of the 19 cases, the color index averaged 1 11 and the volume index was above 1

Boggs and Padget found in their study of 102 cases that the anemia which was found in 81 cases (80 6 per cent) was of moderate degree and was secondary in type, with the hemoglobin about 75 per cent and erythrocytes 3 5 to 4 millions In only two cases was an eosinophilia noted

The leucocyte count is usually normal, except when there is associated secondary infection as in the patients with pustular eruptions

A relative increase of mononuclear lymphocytes has been reported, but in 1910, E M Mason in a study of the blood in 20 cases was unable to confirm that finding Mason also called attention to the fact that eosinophilia, which had been reported in some of the cases when pellagra first appeared in endemic form, was the result of uncinariasis or other intestinal parasitic diseases so frequently found in pellagrins

The Stomach Contents—In 1910 Clarence Johnson, of Atlanta, examined the stomach contents in a series of pellagrins and found that a large proportion of them had achlorhydria Since then many observers have verified Johnson's findings My experience has shown that in most of the mild cases, and in the early stages of even the more severe types, there are mild degrees of hypochlorhydria, but in the severe and neglected cases achlorhydria is the rule

An extensive study of gastric analysis in pellagra was made by Mulholland and King They made gastric analyses in 107 patients with typical endemic pellagra, admitted to the University of Virginia Hospital during a period of eighteen years In 30 cases free hydrochloric acid was present in the stomach contents while in 77 cases there was achlorhydria They found after repeated gastric analyses that the anacidity was permanent but that in a few cases some degree of normal gastric function returned

Busman, of Pittsburgh, reported achlorhydria in 21 of 23 cases in which gastric analysis was made Perhaps the reason for the high percentage of achlorhydria in Busman's cases was that he was dealing with a relatively large number of cases of alcoholic pellagra In Boggs and Padget's series of 102 cases, 90 per cent, in which the gastric contents were recorded, showed an absence of free hydrochloric acid, and it was low in the remainder It should be remembered that Boggs and Padget were dealing with old neglected cases, many of the patients were alcoholics in whom achlorhydria is to be expected even if they did not have pellagra

In Sydenstricker and Armstrong's review of 440 cases, 274 patients had test meals Achlorhydria was found in 180, 43 of whom did not recover (23 9 per cent), and in 67 there was some free hydrochloric acid, 6 (8 9 per cent) of whom died It

is apparent from this study that the determination of the absence of and the degrees of gastric acidity in pellagrins is of importance in prognosis Achlorhydria, however, is a frequent condition, occurring often without symptoms in nonpellagrins It therefore is of no value as a diagnostic aid in pellagra

Examination of Feces—There are no characteristic macroscopic, or microscopic, findings in the stools of pellagrins Since the great majority of cases of endemic, or epidemic, pellagra occur in regions where soil pollution is practiced ankylostomiasis amebiasis and flagellate infestations have been found in many pellagrins Microscopic examination of the feces will reveal such complications when they exist, and when found they should be treated promptly and effectively

Routine Wassermann Tests—Routine Wassermann tests should be made on pellagrins A small proportion of white, and a larger proportion of negro pellagrins, also have syphilis Prompt and adequate antisyphilitic therapy is important, even from the beginning of the treatment of pellagra when two or more positive Wassermann tests or an acknowledged initial lesion, make it certain that the pellagrin is also syphilitic

Porphyrinuria—Hans Fischer developed a test for *porphyrinuria* which was found to be positive in the urine of patients who had active pellagra but after clearing up the symptoms by the use of nicotinic acid, brewer's yeast, and liver extracts what was thought to be porphyrin disappeared from the urine of the clinically cured pellagra patients Spies Sasaki, and Gross made extensive studies on porphyrinuria of 20 pellagrins and tested the urine of 30 normal persons as controls Increased porphyrinuria was found constantly in pellagrins, and the urines of normal persons were free from porphyrin Spies and his associates concluded as follows

(1) ' These studies show that increased porphyrinuria is an integral part of the pellagra syndrome and its presence can be used as an early objective test

(2) These studies show however that the amount of porphyrin in the urine does not parallel the severity of other manifestations of pellagra

(3) ' The administration of nicotinic acid to pellagrins in relapse heals the alimentary tract of pellagra induces blanching of the areas of dermal erythema reduces the porphyrinuria to normal and is followed by a disappearance of mental symptoms

(4) "These findings suggest that a lack of nicotinic acid may be a factor in the development of pellagra and impairment of liver function, with the result that coproporphyrin III is formed in large quantities

(5) 'Coproporphyrin I and III are mild sensitizing agents and may account for the photosensitization observed in some pellagrins "

Beckh, Ellinger and Spies modified Thiel's colorimetric method of determining the presence of porphyrin, or copro porphyrin, in the urine Their technique is as follows

> A measured portion, 10 c c of urine, is put into a separatory funnel and is acidified with glacial acetic acid (about 0 2 c c) to a pH of 4 0 Fifteen to 20 c c of ether are added, and the mixture is shaken for several minutes to insure complete extraction of the porphyrin The lower aqueous layer is separated out and the ether portion is washed twice with 10 to 15 c c portions of distilled water To the ether extract is added 3 c c of 25 per cent HCl The mixture is shaken and then is transferred to a test tube in which the acid and ether layers are allowed to separate The hydrochloric acid portion is examined for porphyrin content In positive specimens the acid layer is colored from pink to purple "

McAnally, Smith, and Perlzweig, at Duke University, using the method of Dobriner and his associates for determining the amount of coproporphyrin in the urine and feces, found an increase in the coproporphyrin content of the urine and feces in untreated pellagra patients, and after treatment with liver extract and yeast the amount of coproporphyrin decreased both in the urine and in the feces Ruffin and Smith called attention to a similar increase of coproporphyrin in the urine in lead poisoning, cirrhosis of the liver, arsenical dermatitis and poison ing with cinchophen, sulfonal and trional It is significant that in most of these conditions there is known liver damage It therefore seems possible that the cause of an increase of coproporphyrin in the urine is liver insufficiency

Spies and his associates suggested that nicotinic acid defi ciency may impair liver function, resulting in abnormal por phyrin metabolism Spies may be correct in his statement that an inadequate amount of nicotinic acid in food may impair liver function and it seems probable that impaired liver func tion may be the cause of the nicotinic acid deficiency and the in crease in porphyrinuria It also occurs to me that the test for coproporphyrin in the urine may be a good method of determin ing liver insufficiency

Sydenstricker is under the impression that porphyrin is but a small part of the reacting substances found in the present methods of examining the urine as a test for pellagra, but he considers the test reliable and of value in making the diagnosis of pellagra. It is agreed that the so called porphyrin test of the urine is an important aid in the diagnosis of pellagra, particularly in the subclinical cases, without skin lesions.

Tests for Nicotinic Acid in the Urine—Vilter, Spies and Matthews have attempted to develop a test for nicotinic acid and its derivatives in the urine. They described their method and reported their results in 1938. They estimated that normal persons on a diversified diet excrete the equivalent of 20 to 50 mg of nicotinic acid, or its conjugates daily, while pellagrins "excrete little, if any, color producing nicotinic acid derivatives." The tests for nicotinic acid and its derivatives in the urine cannot be said to have been perfected and simplified to the extent that they can be of use as an aid in the diagnosis of pellagra.

Research workers in the Biochemical Laboratory at Duke University could not confirm the results reported by Vilter, Spies, and Matthews, in applying their published tests for nicotinic acid and allied substances in the urine. Vilter, Spies and Matthews are continuing their studies, and Perlzweig and Levy at Duke University are working on methods for determining the nicotinic acid content of urine.

Hypoglycemia—Low blood sugars have been observed in pellagra, but that is not of diagnostic significance. A Georgia physician, whose name cannot be recalled, wrote me several years ago regarding a case in which spontaneous hypoglycemia was present. Low blood sugar readings have been found in several patients with pellagra who were treated in the Seale Harris Clinic. In one case an undernourished girl who had distinctive hypoglycemic symptoms and a typical hyperinsulinism curve in a six hour glucose tolerance test developed a pellagrous dermatitis on the parts of her feet and legs exposed to sunlight. Sore mouth, mild gastrointestinal and nervous symptoms developed concurrently after exposure to sunlight. The parts of the feet covered by her slippers were not affected.

It would seem that in the cases of pellagra in which liver insufficiency is a factor there would be deficient glycogenesis In such cases if the islet cells of the pancreas are functioning normally and the supply of liver glycogen is decreased, there should be hypoglycemia (relative hyperinsulinism) It would seem worth while for someone doing research work on pellagra to make six hour glucose tolerance tests on a series of pellagra cases Three hour glucose tolerance tests are sufficient in making the diagnosis of diabetes mellitus (hypoinsulinism), but they are of little value in establishing a diagnosis of spontaneous hypoglycemia (hyperinsulinism) unless they show low blood sugar readings In the latter condition the blood sugar curve may be normal for three or four hours and then drop to very low readings in the fifth and sixth hours, when the hypoglycemic symptoms of which the patient complains are reproduced

CHAPTER XXII

DIFFERENTIAL DIAGNOSIS

The diagnosis of pellagra in communities in which the disease is known to prevail is not difficult, and a typical case in any locality may be diagnosed positively, but when there are no skin lesions it may be exceedingly difficult to be certain that one is dealing with pellagra. The most frequent diseases and conditions with which subclinical pellagra may be confused are (1) sprue (2) pernicious anemia (3) tuberculous enteritis, (4) chronic pancreatitis, (5) gastrogenic diarrhea, (6) stomatitis from various causes.

Sprue.—There should be no difficulty in differentiating pellagra from sprue when the pellagrin has the pigmented or parchment like skin on the dorsal surfaces of the hands, feet, elbows, and on the neck, but it may be almost impossible to differentiate sprue from subclinical pellagra. Indeed there are those notably Burnett, who regard sprue as a manifestation of pellagra, and Jackson believes sprue to be a part of a syndrome in pellagra and other tropical diseases in which diarrhea is a symptom.

Usually, but not always, there are differences in the stomatitis of pellagra and sprue. In the former the buccal mucous membranes are more involved, there is often ulceration of the gums and inner surfaces of the cheeks and the burning "scalded" sensation in the mouth of the pellagrin is often a distressing symptom. The broad tongue in pellagra is often fiery red while in chronic sprue the contracted smooth fibrous looking tongue is characteristic.

The diarrheas of sprue and pellagra are usually quite different. In the former the voluminous foamy, mushy, or pasty stools consist largely of fat and contain many undigested meat fibers while in pellagra the stools are small, frequent, and contain but little fat. The burning in the rectum and vagina in pellagra is also more pronounced. The mental depression in pellagra is usually more pronounced and there is greater tend

ency to psychotic disturbances in pellagra than in sprue, though sprue phobia amounts almost to melancholia with the victims who have seen the severe cases of sprue in the tropics It is questionable if the diagnosis of pellagra without evidences of skin lesions is justifiable except in communities in which it is known to be endemic Indeed, it seems probable that many of the reported cases of pellagra without skin lesions, in which the



Fig 51 —Irregular areas of dermatitis and pigmentation of wrists

predominating symptoms are stomatitis and diarrhea, are really cases of sprue Careful questioning of a pellagrin will usually elicit a history of sunburn on the backs of the hands during the exacerbations of stomatitis and diarrhea, and usually, if there has been any eruption in pellagra, the skin over the olecranon processes at the elbows is thickened, rough, and pigmented Bass thinks that the skin changes on the elbows constitute the most certain and constant lesion in pellagra

Edgar A Hines Jr, of Spartanburg, South Carolina, expressed the opinion that many cases of sprue are being overlooked and treated as pellagra He reviewed the investigations of Wood, of Wilmington, North Carolina, who proved that sprue is not uncommon in the United States Hines called attention to the similarity of sprue to pernicious anemia It will be recalled that Wood suggested the possible common origin of sprue, pernicious anemia, and pellagra It is interesting to note that the classical case of sprue reported by Hines occurred in the son of a woman who had pellagra and had recovered several years previously Pronounced anemia (hemoglobin, 25 per cent, red blood cells, 1,250,000), associated with sore mouth and diarrhea, and several large mushy stools a day, was an outstanding manifestation of Hines' case of sprue

Pernicious Anemia—Pellagra, without marked anemia, does not in the least resemble Addisonian anemia, any more than pernicious anemia without stomatitis or diarrhea presents symptoms of pellagra However, occasionally it is difficult, and at times impossible, to differentiate between pellagra with profound anemia without skin lesions and pernicious anemia with stomatitis and diarrhea Stomatitis and diarrhea are present in practically every case of advanced pellagra, while in pernicious anemia they occur less frequently William Hunter stressed stomatitis as a symptom in Addisonian anemia, and his description of the oral lesions might apply to pellagra so the two diseases cannot be differentiated by the tongue lesions and other mouth pathology

Cabot states that 50 per cent of his patients with pernicious anemia had diarrhea Diarrhea has not been a frequent symptom in my cases of pernicious anemia, but it does occur, particularly in the patients who have not been taking hydrochloric acid or among those who try leaving off the acid after having used it for some time The diarrhea of pernicious anemia is not characteristic It usually is mild in pernicious anemia, but the stools, both in pellagra and pernicious anemia, are small, frequent, and watery, containing much undigested food

The geographic distribution has some bearing in making a diagnosis in cases of stomatitis, diarrhea, and severe macrocytic anemia without skin lesions Pernicious anemia may be seen

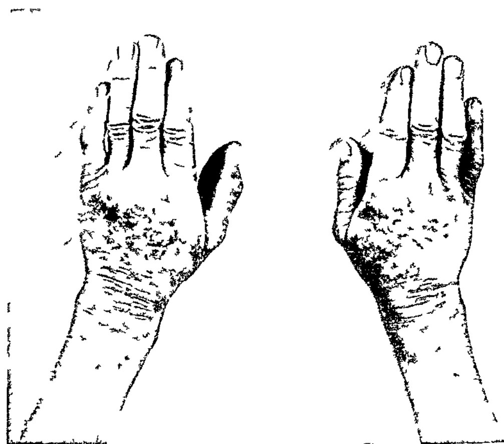


Fig 52—Thickened pigmented skin on backs of wrists hands and fingers in a chronic case of pellagra Male white aged 56 years (Courtesy of Ruffin and Smith Duke University School of Medicine)



Fig 5[illegible] —Eruption on backs of hands and arms of negro

in any climate while endemic pellagra is largely a subtropical disease The lemon yellow tint of the skin in pernicious anemia differs very much from the sallow cachexia of the pellagra victim Loss of weight, sometimes extreme emaciation, is characteristic of pellagra, while as a rule, there is little or no diminution of body fat in pernicious anemia In pellagra the abdomen is prominent and the walls seem thin, intestinal peristalsis being often visible, while in pernicious anemia there seems to be almost if not quite the normal amount of adipose tissue in the abdominal walls The anemia of pellagra is usually of the secondary type and appears after the alimentary tract symptoms are pronounced, while in pernicious anemia the blood changes may precede the stomatitis, and diarrhea may then occur Finally, neurologic symptoms due to cord changes are more frequent in pernicious anemia than in pellagra

Tuberculous Enteritis —Sore mouth associated with diarrhea may occur in tuberculous enteritis but it should not be confused with pellagra, because in tuberculous lesions of the intestines there are associated rapid pulse, daily rise of temperature, and sweats, and in addition, usually there are demonstrable evidences of pulmonary tuberculosis In tuberculous enteritis the stools are small, frequent, and watery, and not infrequently there are occasional small or even large hemorrhages Likewise, usually there are ascites, pain, tenderness and other evidences of chronic peritonitis associated with tuberculous enteritis, symptoms that do not occur in pellagra

Chronic Pancreatitis —The symptoms of chronic pancreatitis are vague and indefinite, but steatorrhea, sometimes associated with diarrhea, is an important finding The stools are large, light colored, and pasty I have treated a few diabetics who developed stomatitis, diarrhea, and severe anemia, in which I believe the essential lesion was chronic interstitial pancreatitis Another patient had sore mouth and tongue, diarrhea, with fatty stools, achylia, marked secondary anemia, loss of weight and strength, and some abdominal discomfort but no actual pain and marked cachexia Scrapings from the tongue showed the fusiform bacilli and the spirilla of Vincent's angina, and the x ray showed a tumor of the pancreas In this case there

were two independent lesions One apparently produced the stomatitis, while insufficiency of the external secretions of the pancreas was the cause of the steatorrhea

Gastrogenic Diarrhea —Stomatitis associated with diarrhea of gastric origin may produce the symptom syndrome of mild or subclinical pellagra Achylia gastrica usually is found in such cases and the symptoms subside in a few days when the patient is given large doses of dilute hydrochloric acid combined with a well balanced, rich vitamin diet Some of these



Fig 54 —Bilateral eruption on backs of hands and arms, more pronounced on and above elbows

cases resemble pellagra very closely and perhaps a small proportion of them are really subclinical pellagra Usually the diarrhea of gastric origin is watery and contains many particles of undigested food with but little fat In gastrogenic diarrhea the emaciation and anemia are not pronounced as a rule though at times there is considerable wasting, with marked anemia in the long standing cases An incidental stomatitis in such a case may make it resemble subclinical pellagra I have seen several such cases in which it was difficult to say that they were not pellagra



Fig 55—Irregular, pigmented thickened areas of skin on backs of hands and above elbows

Stomatitis—A diagnosis of pellagra from the mouth lesions alone is not justifiable generally, though the person residing in a pellagrous locality who has an unexplained stomatitis with a fiery red fissured tongue may be considered a pellagra "suspect" Likewise the alcoholic who complains of sore mouth should be warned that the continuation of any beverage containing ethyl alcohol may bring on pellagra Spies and Blankenhorn, in studying 200 alcoholics who had pellagra, or symptoms suggesting pellagra, found that stomatitis was the first manifestation of pellagra in many cases



Fig 56—Diffuse eruption extending from fingers to above elbows

Vincent's Angina—Vincent's angina "trench mouth" since the World War, is probably the most frequent cause of stomatitis in adults in the United States As a rule, in Vincent's angina, the gums, floor of the mouth fauces and pharynx are most affected, sometimes however the tongue and buccal mucous membranes are involved when it may produce a picture much like the sore mouth of pellagra Spies and his associates found the Vincent's organism in the mouths of pellagrins, and as the mouth lesions cleared up after the use of nicotinic acid, the spirilla disappeared Therefore, if scrapings from the tongue gums, and affected parts show fusiform bacilla and

spirilla, it does not necessarily mean that the patient has not pellagra. It also should not be forgotten that these organisms are sometimes found in normal mouths.

Scurvy.—Stomatitis, sometimes of unknown origin, may be due to scurvy. It may involve the whole mouth with symptoms suggestive of pellagra. Ulcerative patches on the mucous membranes may be found in scurvy. The gums are swollen, ulcerated, and bleed freely, and often there is enlargement of the glands of the neck. The tongue may also be involved in scurvy, and diarrhea is not unusual. In mild cases of scurvy the mouth symptoms generally are more severe than in pellagra. The pain in the epiphyses of the long bones, due to subperiosteal hemorrhages, and the purpuric spots over the body in scurvy when present make it easy to differentiate it from pellagra, but in some cases the stomatitis of scurvy occurring in an individual, who is poorly nourished and who has diarrhea and other digestive disturbances, may resemble subclinical pellagra so closely that a positive diagnosis may be impossible.

Pellagraphobia.—The newspapers and magazines have had so much to say about "the scourge of the South" in the last few years that the public has become pellagra conscious. Many neurotics who develop symptoms of every disease they read about are treating themselves with nicotinic acid for pellagra. Others consult physicians because they fear they have the "red death," as one pseudoscientific editor of a chain of newspapers called pellagra in a recent lurid account of the disease.

The South passed through an epidemic of pellagraphobia about twenty-five years ago when a flood of propaganda was sent out from Washington, with the best of intentions, to awaken the South to the need of preventing pellagra. At that time I was editor of the *Southern Medical Journal* and felt called upon to prepare an editorial on pellagraphobia. The differential diagnosis between pellagra and pellagraphobia discussed in that editorial seems worth reproducing during the present epidemic of pellagraphobia.

Pellagraphobia

"Pellagraphobia seems to be spreading while the disease itself is decreasing except in a few localities. The widespread publicity originating in Washington, regarding 'famine and plague in the South' to

which has been added the advertisements of fake pellagra cures, has inspired in the minds of many a dreadful fear of pellagra The neurasthenics in particular, who are imbued with the idea that their maladies are new and serious diseases have become pellagraphobiacs During the past two months many Southern physicians have had patients who diagnosing their cases as pellagra have sought medical advice Indeed there seems to be much more pellagraphobia than there is of pellagra

"Pellagra being the most discussed disease that exists in the South, physicians in the districts in which there are cases are on the *qui vive* for it and when a patient complains of anything that resembles any one of the so called pathognomonic triad of symptoms i e diarrhea dermatitis and dementia he stands in danger of being pronounced a pellagrin The victim of gingivitis especially if the tongue is involved, whether it be simple aphthous stomatitis or dental infection, is in imminent peril of the 'Southern plague' while the man or woman who has a subacute gastroenteritis with epigastric distress and diarrhea or constipation is often miraculously cured of pellagra by some astute diagnostician Those who drive Fords during the summer and get the backs of their hands sunburned even the doctors themselves are swelling the lists of reported cases of pellagra

"Insanity is decreasing on account of the Washington epidemic of pellagra because it is comforting to the relatives and friends of the victim of any form of the psychoses to know that he is suffering from a fashionable disease instead of a condition that is supposed to stigmatize the family name Likewise the widely heralded increase in pellagra has reduced the incidence of chronic malaria, which was formerly the convenient and satisfactory diagnosis for every chronic condition which could not be accounted for in any other way Tuberculous peritonitis and enteritis and the subacute and chronic dysenteries both bacillary and amebic uncinariasis sprue and other diseases in which diarrhea is a symptom are also among the conditions which have recently been diagnosed incorrectly as pellagra

Perhaps the condition which is most frequently diagnosed as pellagra is the toxic often the terminal stage of chronic nephritis in which there is a dry red tongue nausea vomiting diarrhea delirium and prostration The fact that there is little or no albumin in the patient s urine and that there are few of the usual symptoms of nephritis is misleading and the puzzled doctor hits upon the diagnosis of pellagra which accounts for the symptoms and satisfies the anxious relatives, who regard pellagra as a necessarily fatal disease

"DIFFICULTIES IN THE DIAGNOSIS OF PELLAGRA — The Journal does not intend to reflect upon the diagnostic ability of the physicians of the South because they are as well prepared to practice their profession as are the doctors of any other part of the country but it must be admitted that all of us make mistakes and when one is looking for a disease he is prone to find it particularly if his patient has suggestive symptoms

"Much has been said about prepellagrous symptoms early pellagra atypical pellagra, *pellagra sine pellagra*, and parapellagra, and un

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doubtedly many of us have erred in diagnosing conditions as pellagra that really have little resemblance to the disease. It is easy to diagnose the typical well developed case of pellagra in which there is sore mouth, diarrhea, bilateral dermatitis on the backs of the hands, and mental depression, but sometimes the symptoms are not so pronounced and the diagnosis is more difficult. The skin lesions are most characteristic, as the name pellagra indicates, and one cannot be positive of the diagnosis without the dermatitis, unless other members of the same locality, living under like conditions, or in the same environment, have the classical symptoms.

"The physician should be careful in reporting pellagra. He should report to the state board of health every case in which he is certain of the diagnosis, just as he should every case of tuberculosis in which there is no doubt of the nature of the disease. If, however, there is doubt of the diagnosis the case might be reported as suspicious of pellagra giving the symptoms upon which the conclusions are based, and the statistician of the state board of health could announce the number of positive cases and number that have symptoms suspicious of pellagra."

The brilliant, and revered George Dock, when Professor of Medicine in Tulane University, was one of the early students of pellagra. In 1912 in an article on "The Early Diagnosis of Pellagra," Dock called attention to the early symptoms of pellagra, which, if studied carefully, would enable the physician to make the diagnosis of pellagra before all the triad of classical symptoms appeared. The following excerpts from Dock's paper published in 1912 apply in the diagnosis of pellagra in 1940.

"The possibility of sunburn, exposure to water or to irritating liquids, to heat or ultraviolet rays, must be investigated. The differences of the extent of sunburn and pellagra on uncovered parts must be borne in mind as well as the atypical localization in covered parts.

"The possibility of toxic erythemas must be borne in mind—in such cases as those described as acrodynia, cereal intoxication, drug eruptions, ergotism and vasomotor or trophic changes in diseases of the nervous system. Alcoholic neuritis, for example, is said to be associated at times with erythema, especially in the spring, and evidences of nerve changes should be sought for in all cases of pellagra. It must be remembered that the pellagra erythema occurs especially in spring but also almost as frequently as late as September or October. In Louisiana a surprising proportion of patients give August or September as the time of beginning. The assisting causes, such as exposure to sun and associated symptoms, should be elicited in such cases. While faint signs such as desquamation, pigmentation or atrophy, may persist after the erythema, it is important to remember that in such cases, even after several years of recurrent erythema, the skin in the intervals

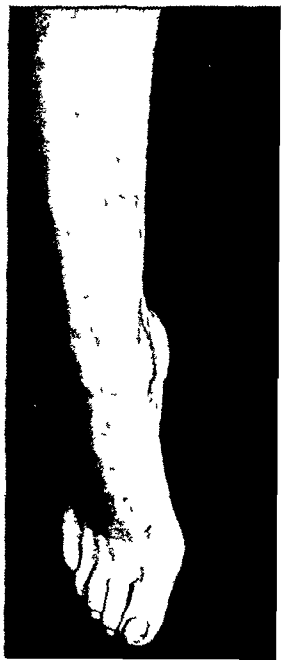




Fig 58 —Diffuse erythematous eruption of feet and ankles Note bullae on both feet

shows no discoverable anomaly This is stated by various authorities, and I was able to see many examples in the pellagra hospital in Rovereto, Tyrol The rapidity of recovery of even severe lesions some times is itself very suggestive

"The symptoms on the part of the alimentary canal deserve more care than they usually receive It is true of most diarrheal diseases that they receive less careful diagnosis than the present knowledge of such cases suggests, not only in the serious chronic cases of amebic enteritis, but also in the gastrogenic diarrheas of all grades of severity Pellagra with its frequent diarrhea and its remarkable though variable stomatitis, shows the importance of a complete examination of the alimentary canal from the lips to the anus, with a no less careful examination of the stools In this part of the work many indications for treatment are likely to be met "

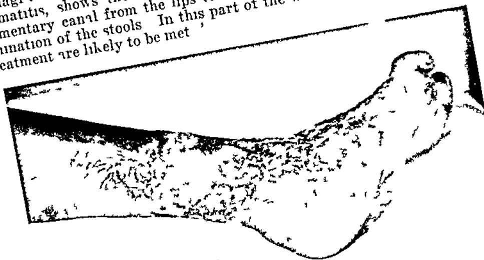


Fig 59 —Asymmetrical lesions of right foot and leg The left foot was normal

The Differential Diagnosis of the Skin Manifestations in Pellagra From Other Dermatoses—Cosby Swanson, a dermatologist of Atlanta, published an excellent article on the diagnosis of pellagra from the skin lesions Excerpts from Swanson's paper make a valuable addition to a chapter on the "Differential Diagnosis in Pellagra "

"The following diseases often have skin manifestations that resemble the eruption of pellagra acrodynia erythema solare erythema calorieum erythema pernio erythema multiforme eczema especially the erythematous form, dermatitis venenata 'recurrent summer eruptions,' lupus syphilis xeroderma erysipeloid, erysipelas

"The skin manifestations in pellagra present three stages congestion thickening and pigmentation and atrophic thinning The eruption often begins as a macule which lasts for several days and in some cases several weeks In most cases the lesions fuse in a very short

time, forming a patch of livid red erythema covering a large area The erythema may reach its height of development suddenly, but as a rule it does not for several days

"In acrodynia (erythema epidemicum) the skin manifestations are like the eruption seen in pellagra in many ways It usually begins as an edematous swelling of the hands, feet, and face, followed by an erythematous rash upon which vesicles and bullae develop As the erythema subsides there is exfoliation of the epidermis leaving the skin thickened and pigmented The other symptoms of the disease are indigestion, diarrhea and depression, but usually of a short duration The rash is unlike pellagra, in that it runs a shorter course, rarely ever recurs and is a very rare disease in this section

"In some cases the erythema from the exposure to the sun is very severe, causing an acute erythematous rash of a bright red color, often forming vesicles and bullae The acute eruption is followed by exfoliation of the epidermis, later pigmentation takes place The severity of the dermatitis from the sun depends largely upon the season the duration of the exposure, sensitiveness of the skin, condition of the person's health The reaction is more marked in persons suffering *from any toxic condition*

"The erythema from a sunburn presents, on close observation, several features which distinguish it from pellagra In this condition the area is usually less acutely inflamed there is less redness, and gradually fades instead of becoming darker, as does pellagra, and is followed by less exfoliation of the epidermis and very little pigmentation

"The skin manifestations in erythema multiforme often assume many of the characteristics of the eruption of pellagra *The lesions that are* usually seen in erythema multiforme are macules, papules, nodes, with the occasional appearance of vesicles and bullae The lesions in the beginning are usually discrete occurring in groups, some cases fuse later and cover large areas The rash occurs bilaterally on the hands, forearms, neck chest and lower limbs, occasionally on the face and body The eruption assumes a crimson red or a purplish red color

"*Erythema multiforme is like pellagra, in that it is* prone to recur, usually is seen in the spring and autumn, and is accompanied by nervous and gastric intestinal symptoms It differs from pellagra, in that the eruption is found on the flexor more often than on the extensor surface and seldom on the face and other parts of *the body that have* not been subjected to irritants The eruption as a rule is more edematous than in pellagra The duration of the lesions is usually short, lasting from a few days to two or three weeks"

CHAPTER XXIII

PELLAGRA IN CHILDHOOD

By Katharine Dodd, M.D., Nashville, Tenn.

Introduction.—Pellagra may occur at any age during infancy and childhood but is recognized with frequency from about the age of five years. Statements in the literature vary as to whether the disease is more common in adults or children, but the majority of authors agree that it occurs about eight to ten times as often in adults, partly because there are more adults than children. The malady is seen in the southern part of the United States oftener than in the northern, eastern, or western sections, but there are reports of cases of pellagra from all parts of the country. Although at times the dietary deficiency develops secondarily to some other disease or congenital abnormality, most of the reported cases are those of a primary lack of sufficient pellagra preventive factor in the diet.

Age Incidence.—That pellagra occurs at birth has not been conclusively demonstrated. Snyder[1] sent out a questionnaire to 60 physicians in 1912, and asked for the age of the youngest child in whom each physician had observed pellagra and whether he had any evidence that the disease could be carried from mother to child through the agency of the mother's milk. The youngest observed case was in an infant of two months, and of the children reported 5 were under one year of age. Nine physicians had seen pellagrous mothers who were nursing infants without any evidence of the disease being seen in the infants. The case of the two month old baby was reported to Snyder by Savage of Alabama. He wrote that a two months' baby nursed a pellagrous mother for four weeks. The baby was then fed malted milk. The mother died of pellagra when the infant was six weeks old. "The erythematous rash did not appear until several days after the mother's death, but I was informed by the midwife that the infant was much emaciated at birth and had been affected with a profuse, foul smelling diarrhea since one week old." It sounds as if this were a case of congenital pellagra. Weston[2] reports an instance

problem in infant nutrition or are the journals dominated by men from the north?

Skin Manifestations.—Pellagra in childhood often presents a different picture from that of the usual adult type. Skin manifestations in a large proportion of children are the most marked signs of the disease. The erythema appears suddenly and, since it usually is seen after exposure to sunlight, is often mistaken for sunburn. There is usually swelling of the affected part. Itching is mild or absent but pain and burning may be complained of. In older children the hands and the feet are most often affected but in infants the eruption frequently appears first on the face, either over the nose or about the corners of the mouth. The lesions are always symmetrical and on the extremities have a sharp border. The neck is a frequent location for the eruption in children. The back of the neck is uniformly involved, but there is a small pale thin skinned spot where the chin shades the skin of neck and upper chest. Later the skin becomes darker, rough, and thick or may form blebs and blisters. Except for the lack of itching, the line of demarcation, and the greater degree of pigmentation in the late stages, the eruption is almost identical with that of infantile eczema. In the negro the pigmentation and thickening of the skin is very marked. Two children with skin eruptions on their necks, but with little other evidence of pellagra, told the nurse, who was giving them a bath, "Perhaps if you tried turpentine all that dirt would come off. Mother has tried and tried but she can t do any good with soap and water." In some cases the dermatitis spreads over the entire surface of the body. The skin of the body is then usually not so swollen and red in the early stages and not so deeply pigmented later as that of the extremities, neck, and face. Cases of this kind, especially when there is no marked symmetrical dermatitis of the hands, feet, or neck, may be very difficult to differentiate from the xerosis of vitamin A deficiency or from mild ichthyosis.

Stomatitis.—As a rule children complain little of sore mouth when they have pellagra. On examination the tongue may be coated, with red edges, or there may be some ulcerations or blisters. Most of the children we have seen had normal mouths or slightly increased reddening of the tongue and buccal mucosa

Diarrhea is frequently complained of and, as already stated, may be the presenting symptom or the first symptom of the disease It was present to a greater or less degree in over one half of our children, and in one case was severe enough so that it and the vomiting very nearly caused the death of the child The diarrhea usually consisted of frequent watery stools, but in several instances blood appeared in the feces late in the disease The girl who nearly died of diarrhea and dehydration had ulcerative colitis which started with her second attack of pellagra and has persisted in a mild form for ten years Two of our patients had bloody diarrhea at the onset of the disease, but here it seems altogether likely that the primary disease was bacillary dysentery and the pellagra, or at least its clinical manifestations, was secondary to the poor nutrition, caused by the dysentery Many of our children were too young to do much complaining or if they did the parents forgot to mention it One mother told us that her child had said he felt a fullness of his stomach, and four children had belched a great deal and occasionally vomited Except in two very severe cases the appetite remained fairly good

Nervous Symptoms—Psychoses evidences of spinal cord involvement, and tremors of the tongue or extremities were not usually encountered in the children with pellagra However the parents often mentioned fretfulness or nervousness We have heard many such complaints as, "He is moody and cries easily," "He takes no interest in school and is losing his memory " "He is stuporous and his mind is off at times " "He has lately become very difficult to manage " One child had an attack of trembling for several days before the onset of diarrhea one seemed to have spells of blindness and one girl of fifteen felt " as if she were bound up in yarn " This last patient later in the summer had signs of combined sclerosis of the cord and a psychosis She prayed, swore, removed her clothes, screamed, and became quite unmanageable She had had pellagra for at least ten summers Nervous system symptoms are usually late in developing and are seen in a severe form only after the patient has had the disease for years

Family History—Frequently in the past whole families have been affected by pellagra In our series one fourth of the parents

gave a history of the disease in other members of the family or themselves had pellagra. One child's mother had died of pellagra, the father was ill with it at the time, and five other children also had it. In another family the three eldest children died of pellagra at ten, seven, and five years of age, our patient had it in a severe form, yet the three children younger than he had no signs or symptoms of the disease. We have not ourselves lost a child with pellagra. Most of them have had one or more relapses even after we have seen and treated them with brewers' yeast. They take the yeast until the skin eruption disappears and the diarrhea slows up, continue with the old diet, and return with pellagra again the next spring and summer. The greatest number of known relapses occurring in any child was ten, though some children of twelve or more were said by their parents to have had diarrhea and a skin eruption every year of their lives. Such children were very small for their age and markedly undernourished.

Most of the diets recorded as being taken by the children were poor. One child lived mostly on potatoes and fried pies, another on oats, fried potatoes, and corn bread, and a third on fat meat, beans, and corn bread. In four instances, the diet was excellent as far as we could determine but in one of these when the child returned to the out-patient department after he had been cured in the hospital, the parents confessed that, though the child had been offered a good diet, he had never eaten well at all. A few of the children undoubtedly developed pellagra because of conditions other than the diet offered. One was an imbecile who had never learned to eat, two had probably had severe bacillary dysentery, one had congenital stenosis of the ileum, and one was a Mongolian idiot whose family paid little attention to her. Similar reports may be found in the literature. Ellis[8] writes of a case of pellagra in Boston in a 9 year old boy with tuberculous enteritis. Zahorsky[9] tells of a girl of thirteen who starved herself because of being teased for being too fat. She developed pellagra. Stevens[10] gives the history of a child of five who developed pellagra after being put on a ketogenic diet for epilepsy.

Subclinical Pellagra.—Many authors, among them, Snyder,[11] state that there is no justification for the discussion of "pellagra sine pellagra" in childhood. Bloom[12] writes "In my researches

I have seen some children who presented the general symptomatic picture of pellagra but did not exhibit any cutaneous manifestation of it They were children of varying age, who gave indications of progressive prostration, of heaviness of head vertigo were sad, irritable, very excitable, with tremors both of the tongue and of the extremities, pains in the back, exaggeration of reflexes and diarrhea The onset, the course of these symptoms illustrated the pellagra periodicity " Seven of the children in our series gave a history of marked diarrhea either preceding the development of skin lesions or occurring the summer, or the two summers, before the occurrence of the typical eruption Several children seen in the clinic with diarrhea of unexplained origin later returned with typical cutaneous manifestations of pellagra

Multiple Deficiencies—One of the difficulties encountered in an attempt to describe symptoms and signs of any vitamin deficiency is that in the human being a single vitamin lack, the rest of the diet and the digestion staying normal, is almost never found, although some children with pellagra are well nourished, apparently feel well, and have only the characteristic skin lesions with perhaps a slight diarrhea, this is often not the case Lewis[7] described a poorly fed, colored child of seventeen months with pellagra, rickets, nutritional edema, and probable beriberi and scurvy One child in our series had tetany Six had nutritional edema of a severe grade All of our children who had edema had a low percentage of serum albumin in the blood Such hypoproteinemia with or without edema is common without evidence of pellagra preventive factor deficiency among our hospital and out patient clientele[14] A low protein, low calorie diet is undoubtedly the usual cause of the condition Three of the children with pellagra were very anemic and most were moderately so Again anemia of greater or lesser severity is almost universal in all of our patients One boy in the series had xerophthalmia and several other children had photophobia and chronic conjunctivitis or blepharitis very suggestive of xerophthalmia Diarrhea is so common in our clinic patients, particularly during the months when pellagra is at its height, that it is often impossible to say whether in a given case of diarrhea, the loose stools are due to the pellagra, a factor in the pro

duction of pellagra, or merely evidence of a concomitant disease I have described what are usually considered the outstanding signs and symptoms of pellagra in children Other manifestations may always be part of other dietary deficiencies

Differential Diagnosis—In the differential diagnosis of pellagra most authors state that the disease is easy to diagnose in children, and then give a table or a discussion of the differential signs and symptoms of acrodynia and pellagra preventive factor deficiency The disease picture of acrodynia is now so well known and the lack of relation of vitamin deficiency to the disease so well recognized, that there is seldom any confusion between the two diseases The present difficulty is to be sure in atypical cases whether one is dealing with pellagra preventive factor deficiency in an unusual form, whether roughening of the skin may not be due to vitamin A lack, mild eczema, or ichthyosis with diarrhea from some other cause, or whether pellagra may be playing a minor role in a disease picture or a nutritional problem primarily due to other causes With our increasing knowledge of dietetics and particularly of the vitamins we no longer find orphanages in which as many as 17 of the children have pellagra and 3 die of the disease[1] Also because of the availability of cheap supplies of vitamin pellagra preventive factor and the increased knowledge of the medical profession as to the course and treatment of pellagra, few severe and long standing cases appear at hospital clinics However, there are still many children in whom the condition goes untreated because their parents do not take them to a doctor and undoubtedly many with little or no skin eruption in whom the disease, while present is not even considered as a possibility It has become a matter of importance to be able to recognize less typical forms of the disease, for it is possible that it may be acutely fatal in infants who are never in the sun and have no skin lesions, that it may contribute to a fatal outcome when there is some other primary disease, or that a chronic deficiency of vitamin pellagra preventive factor may produce great impairment to health, strength, and perhaps mentality without the patient's ever being acutely ill

As yet we have no satisfactory test for insufficient storage of vitamin pellagra preventive factor in the body Since chemical

tests have been available to prove the existence of vitamin D and C deficiencies, we have found that the specific signs and symptoms we recognize clinically as those of rickets and scurvy are late manifestations of the dietary lack. The same will undoubtedly prove true in pellagra.

Treatment.—In many children the symptoms of pellagra are so mild that a change to a good diet is all that is necessary to cure the disease. The addition of brewers' yeast in 2 to 4 Gm. doses three times a day will hasten the cure in most cases and is necessary when the diet cannot be improved. Nicotinic acid in 10 mg. doses for infants and 25 mg. doses for older children three or more times a day now offers a very easy method of obtaining a cure. In severe types of the disease, these doses may be greatly increased or the nicotinic acid may even be administered by vein.

Case Reports.—The following case reports and photographs are illustrative of variations in the pellagra picture which we have encountered.

CASE 1.—Recurrent pellagra producing stunting of growth in a 5 year old boy. Rapid cure with brewers' yeast.

A moderately well nourished though very small, white boy of five years was admitted to the hospital in May 1930 with the chief complaint of a breaking out on hands, face and feet. This breaking out had occurred every spring since he was eight months old. The present attack had existed for two months and had been associated with slight soreness of the mouth for a few days. During the attack the previous spring there had been some diarrhea. His diet had been mostly fat meat, molasses and dried beans with very little fruit, vegetables or milk. He was thirty six inches tall or shorter than any height given in the American Public Health Association tables for a normal five year old boy. His weight was 28 pounds. On admission hands, wrists, forearms, feet and ankles were symmetrically affected, the skin being rough and dry and in places fissured. The color of the lesions varied from a bright red to a dark dirty brown. Around his neck forming a collar was a similar skin change. There was slight dermatitis on the cheeks and across the nose. The mucous membranes appeared normal. The boy was somewhat constipated. He was given a high protein diet, brewers' yeast and cod liver oil. His appetite became good after a few days and the skin began to soften. He was discharged much improved after a stay of nine days. The skin around the neck and over the face was almost normal, that of the hands and feet had cleared only partially. Through the efforts of the social service department the parents were able to continue to give him a fairly good diet at home and on this and continued brewers' yeast he has had no recurrence of his trouble.

Case 2.—*A first attack of pellagra with skin lesions, diarrhea, drowsiness, and irritability in a 5 year old boy. Cure with nicotinic acid by mouth.*

A well developed, well nourished, but drowsy, child, who was irritable when disturbed, was admitted to the hospital in May, 1938. The weather was warm and sunny at the time, and the parents remarked that the boy became active only after sundown. He had been breast fed for eighteen months, and though he had been offered a good diet after he was weaned, he had never taken it well. Two months before the parents had noticed a red area on the skin of the face, extending



Fig. 60.—Diffuse pigmented eruption on nose and cheeks of child pellagrin. Note the Casal's collar.

over the nose and onto the cheeks. Later red spots appeared above the eyes. These gradually spread until the whole face and most of the neck were involved. The lesions on the hands and feet followed in a week or two. Blisters came on the legs and later ruptured. These lesions did not itch and apparently caused no discomfort. Two weeks after the onset a moderate diarrhea of three or more watery, foul smelling stools a day was observed. During the last two weeks blood and mucus had been present in the stools. It was only during the past week that the drowsiness and irritability had appeared. The parents had noticed blisters around the edge of the tongue during the

entire illness They had taken the boy to a physician who had given him some sort of subcutaneous injections and tablets of thiamine chloride to take by mouth According to the parents he had said 'They'll say at Vanderbilt that it is pellagra but it can't be He doesn t get well when he gets the medicine which should cure it" On admission the patient looked and acted as the parents had described He was well developed and moderately well nourished drowsy or irritable by turns He was given a regular diet with 8 25 mg of nicotinic acid in solution by mouth every three hours In ten days the diarrhea had stopped the mouth was well the skin lesions were fading and the



Fig 61 —Eruption on hands and arms of the same child

child was normally active This was the first patient on whom we used nicotinic acid We were not impressed with the rapidity of the results obtained compared to those obtainable with brewers yeast or even with our hospital diet alone

Case 3 —Severe recurrent pellagra in a 14 year old negro girl with edema tetany marked dehydration vomiting and ulcerative colitis Almost complete cure after four stormy months

A 14 year old colored girl was admitted to the hospital in July 1932 with the complaint that her bowels ran off and her jaws locked" Her mother had died the year before with spells ' No details could

be obtained as to the diet Three summers before she had diarrhea all summer The next summer she was well but in the spring of 1931 she broke out with an eruption on her hands and feet and *had diarrhea* again with about 10 loose stools a day The diarrhea had persisted to the time of admission Lately there had been blood in the stools and she had vomited almost everything she ate She said that her mouth had been sore most of the time and that her feet, hands, and neck had been rough and very black at times Of late she had felt too weak and ill to go out and the skin lesions had improved markedly



Fig 62 —Dermatoses of feet and legs of the same patient

The child was of normal height for her age but was emaciated and dehydrated She was extremely apprehensive irritable and unreason able Only on the anterior surface of the legs was there any increase in pigmentation or roughening of the skin There was little evidence of stomatitis In spite of the extreme wasting there was edema of the feet, legs and face Her jaws were stiff and she had carpopedal spasm The hemoglobin was 6 8 Gm, the serum albumin 3 2 per cent The serum calcium was 11 0 mg the pH of the blood 7 29 with an alkali reserve of 39 volumes per cent The guanidine was 1 13 mg per cent in the serum We attributed the tetany to the increased guanidine



Fig [illegible] —Skin lesions in a five year old pellagrin The eruption on the hands, arms, feet and legs is much more pronounced than on the face

We tried to put the girl on a good diet with large amounts of brewers' yeast. All went well for a day or two. Her peristalsis was so fast, however, during this time that tomatoes eaten at noon appeared in her stools three hours later. She soon began to vomit everything. We resorted to continuous venoclysis to keep her hydrated, and after four months of continuous struggle during which we gave numerous blood transfusions, tried all sorts of diets, and managed to make her keep down a large amount of brewers' yeast, she was vastly improved. She still had a diarrhea and had many ulcers in the colon. Now, six years later, she is a well developed, well nourished, pleasant, and cooperative colored girl. The only sign of her pellagra that remains is a mild persistent ulcerative colitis. Had we had nicotinic acid for intravenous injections as we do now, we could doubtless have saved ourselves many hours of work and the girl a great deal of suffering.

Case 4.—Pellagra and nutritional edema with bacillary dysentery as a probable precipitating cause in a 10 month old colored girl. Rapid cure with good diet and brewers' yeast.

A 10 month old colored baby was admitted to the hospital in August, 1936. She was breast fed for eight months and then started on buttermilk with the addition of cereals, potatoes, cakes and crackers occasionally. She had never nursed or eaten well and had vomited often. Three weeks before admission she began having a diarrhea of 10 to 15 stools daily. These stools contained pus and blood. The diarrhea had improved to about 7 stools a day without blood or pus but the baby was restless and irritable. Ten days before admission areas like "chapped places" appeared on her knees and later on her neck, arms and hands, feet and legs. In a few days the lesions became very dark in color. Three days before she came to the hospital the feet and face became swollen. On admission there was a symmetrical, very black thick lesion of the skin involving the face, the neck, arms to above the elbows and legs nearly to the hips. In the creases of the elbows and knees the skin was normal. There were cracks in the mucous membrane at the corners of the mouth. Pitting edema of the legs and feet was marked. The child weighed 11 pounds. She was weak and irritable. The deep reflexes were exaggerated. The hemoglobin was 10 Gm., the serum albumin 1.9 mg. per cent. The baby was given a transfusion, put on a diet of buttermilk, vegetables, eggs, and cereals and given 4 Gm. of brewers' yeast daily. The diarrhea ceased in two weeks, the skin lesions gradually faded and the edema disappeared. Two months later the child was well and happy and was eating a general diet with relish.

Case 5.—Pellagra?, xerophthalmia and nutritional edema in a 3 year old boy. Generalized xerosis of skin due either to lack of vitamin A or pellagra preventive factor.

A 3 year old, white boy was admitted to the hospital in February, 1932, with the complaint of breaking out all over the body, diarrhea, loss of weight, and sore eyes. He was said to have been fed canned milk, fat meat, beans, and bread. Ten months before, the child's eyes had begun to be injected and the light hurt them. A month later he



Fig 64 —Xerophthalmia and nutritional edema in a three year old boy Note the generalized xerosis of the skin over abdomen and arms Questionable pellagra

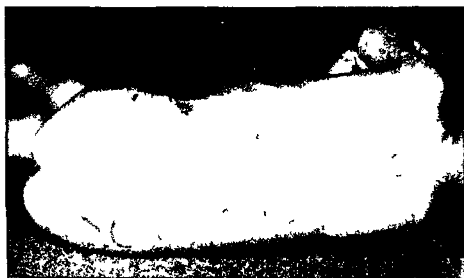


Fig 65 —Generalized xerosis of skin on the back of same patient as shown in Fig 64 Condition was due to vitamin A deficiency or pellagra

had diarrhea without blood in the stools Four months later a rash appeared on his hands, later spreading to his arms, feet, face, and finally to the trunk At times his whole body had seemed swollen and was noted to pit on pressure He often stayed in bed for whole days at a time On admission the child lay shading his eyes with his arms The conjunctivae were injected as well as the sclerae A few small opaque spots were seen on the cornea The boy was undernourished and flabby The skin was everywhere dry, rough, thick, and desquamating There was no symmetrical dermatitis of the extremities The tongue was smooth and red with prominent papillae There was a pitting edema of the feet The reflexes were normal The child weighed 22 pounds The urine was normal hemoglobin 11 Gm, serum albumin 2 8 per cent When first seen, the child was having 6 or more loose watery stools a day With no treatment except a good general diet cod liver oil brewers' yeast, and orange juice he almost immediately began to improve The diarrhea ceased the photophobia cleared up the eyes looked normal the edema disappeared, and the skin became soft and moist In four weeks he had gained 6 pounds and was a fat happy little boy He was boarded out and later adopted because his mother had neglected him and took no interest in him The vitamin A deficiency could explain the skin lesions as we saw them, and the poor feeding and nutritional edema, the diarrhea The history of gradually increasing symmetrical skin lesions makes the diagnosis of pellagra seem probable

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CHAPTER XXIV

THE HEART IN ENDEMIC PELLAGRA*

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There is convincing evidence that nutritional deficiency is intimately concerned with the pathogenesis of pellagra, yet endemic pellagra lacks much of the characteristic clinical behavior of a true deficiency disease

Many of the diseases produced by avitaminosis affect, in a selective manner, certain tissues of the body, and one can anticipate precisely the kind of deficiency by noting the structures involved and the character of the tissue reactions

In an effort to place pellagra more specifically in its relation to deficiency diseases which are known to affect the heart and vascular system, a systematic study of the heart has been conducted on all endemic pellagrins assigned to our hospital wards for treatment during the past five years

Recently in a brief discussion of endemic pellagra, we expressed the opinion that pellagra per se did not significantly affect the heart, and commented upon the universal absence of

Electrocardiograms—Only one patient, Case 25, showed a disturbance of rhythm He was 61 years of age was a chronic alcoholic and had marked arteriosclerosis The electrocardiogram showed an occasional auricular extrasystole

An electrical axis indicating left ventricular preponderance occurred in 3 other patients, all of whom had elevated blood pressure Case 20 had a systolic blood pressure of 190 diastolic 105, Case 24, systolic blood pressure of 160, diastolic 100, and Case 22 systolic blood pressure of 195, diastolic 120

T wave changes occurred in 6 electrocardiograms yet, in only one instance Case 4, could one justifiably relate the alterations to pellagra alone In this patient there occurred an isoelectric TI and a deeply inverted TII and TIII After eighteen days of treatment the electrocardiogram showed a return to normal (Fig 66) This patient was a chronic alcoholic Case 6 showed

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TABLE XVI

CASE	AGE	SEX	PULSE RATE	BLOOD PRESSURE SYS	BLOOD PRESSURE DIAS	MURMURS	TELEROENTGENOGRAM TRANSVERSE DIAMETER CM	TELEROENTGENOGRAM CARDIO THORACIC RATIO PER CENT	ELECTROCARDIOGRAM	COMPLICATIONS
1	21	F	125	110	6[illegible]	None	11 0	[illegible]9	Normal	None
2	22	F	136	128	90	None	11 6	44	Normal	Chronic alcoholism
3	23	F	104	95	65	None	9 0	35	Normal	Otitis media, purulent colitis
4	26	F	125	126	84	None	10 2	43	See chart	Chronic alcoholism
5	28	F	121	105	65	None	12 0	47	Normal	None
6	28	F	107	90	55	None	11 0	44	TI, TII, and TIII isoelectric	Rectal stricture
7	30	F	118	110	76	None	10 5	40	Normal	None
8	32	F	110	135	95	None	12 3	45	Normal	Alcoholism, laceration on skull
9	34	F	115	102	65	None	10 5	44	1 2 36 TII and TIII inverted 1 29 36 TII and TIII isoelectric	Rectal stricture and colitis
10	37	F	102	105	60	None	11 0	45	Normal	None
11	37	F	124	126	85	None	9 8	41	Normal	Alcoholism, neuritis
12	39	F	125	115	80	None	10 0	42	Normal	Alcoholism, neuritis, severe
13	39	M	115	132	82	None	12 0	42	TI isoelectric	Purulent otitis media
14	40	F	115	118	85	None	9 7	38	Normal	Positive Wassermann
15	42	M	109	145	95	None	11 5	38	Normal	Chronic alcoholism
16	43	F	128	110	70	None	10 2	46	TI and TII isoelectric	Death Heart weight 250 grams
17	44	M	100	110	70	None	11 0	37	Normal	Arteriosclerosis
18	46	M	86	125	90	None	10 6	41	Normal	Pyelitis
19	47	M	118	120	80	None	11 0	39	Data lacking	Chronic alcoholism
20	49	M	94	190	105	None	12 5	48	Electrical axis, left *preponderance*	Essential hypertension
21	49	M	96	120	75	None	11 1	34	Normal	None
22	54	M	116	195	120	None	12 9	43	Electrical axis, left preponderance	Essential hypertension
23	59	M	88	160	100	None	14 0	46	Normal	Essential hypertension
24	60	F	107	160	100	None	12 1	44	Electrical axis, left preponderance, TI TII TIII isoelectric	*Arteriosclerosis, diabetes,* psychosis
25	61	M	98	148	70	None	15 0	50	Ventricular extrasystole left preponderance	Arteriosclerosis Alcoholism
Average	40		111	1[illegible]8	81		11 3	4[illegible]		

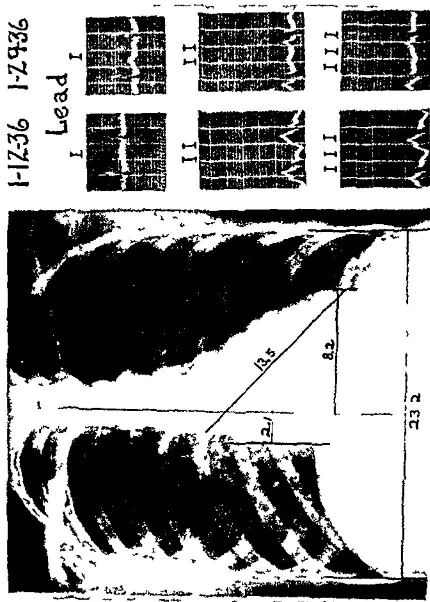


Fig 66.—X ray showing cardiothoracic ratio and electrocardiograms The T wave changes are attributed to B deficiency

an isoelectric TI, TII, and TIII four days before death At the time the electrocardiogram was made the oral temperature was 103 4° F, due to a complicating pyelonephritis Case 24 showed a left ventricular preponderance and an isoelectric TI, TII, and TIII In addition to elevated blood pressure, this patient had diabetes and arteriosclerosis, and was markedly psychotic Case 9 had an inverted TII and TIII which changed to an iso electric TII and TIII when the patient's clinical condition im proved The pellagra was complicated by chronic alcoholism a rectal stricture, purulent colitis, and a positive Wassermann Case 13 showed an isoelectric TI, the pellagra was complicated by a bilateral purulent otitis media

Case 16 showed an isoelectric TI and TII twenty two hours before death when the rectal temperature was 104 4° F Bron chopneumonia was found at autopsy

In summary, 10 patients showed changes in the electro cardiogram Of these 5 had vascular disease 1 purulent otitis media, 1 pyelitis, 1 diabetes, 1 rectal stricture and purulent colitis, and 1 chronic alcoholism In this last patient, one is justified in concluding that pellagra and alcoholism were the factors responsible for the electrocardiographic changes for with clinical improvement, the alterations disappeared

The weights of 14 hearts from patients dying from pellagra, in whom there were no important pathologic lesions involving the cardiovascular apparatus, have been tabulated in Table XVII

TABLE XVII

THE WEIGHT IN GRAMS OF THE HEARTS FROM 14 PELLAGRINS

	AGE	MALE	AGE	FEMALE
	3[illegible]	275	35	225
	65	300	40	225
	59	350	50	210
	30	235	57	300
	65	365	36	327
	25	300	31	250
	58	330	43	250
Average	47	307	41	255

The data show that in this series of cases the average heart weight for the males was 307 Gm and for the females 255 Gm White gives as the normal heart weight for males 300 Gm and for females 250 Gm

Discussion

Feil in a recent report on the electrocardiographic changes in pellagra says

> "Pellagra and beriberi apparently affect the heart physiologically in much the same way The cardiac manifestations in pellagra however are less severe "

The heart in beriberi has been studied extensively by Scott and Herrmann, Wenckebach, and Keefer, and all of these observers have been impressed by essentially the same type of cardiac changes Wenckebach has stressed the fact that in beriberi there is marked cardiac dilatation particularly of the right ventricles, and that the heart is definitely increased in weight He makes the interesting suggestion that the increase in weight is not due to a true hypertrophy, but to intracellular edema of the myocardium brought about by the physiochemical changes induced in the muscle protoplasms by the deficiency state Clinically, heart failure of the congestive type occurs and the failure is predominantly of the right ventricle Marked distention of the veins enlarged tender liver and extensive edema characterized the clinical picture Various alterations have been recorded electrocardiographically in a small percentage of the patients studied, yet all authors agree that the changes are not characteristic or constant Wenckebach makes the unequivocal statement that the electrocardiogram is normal, except that the conduction time is shortened

During recent years we have observed a group of patients who had organic cardiovascular disease and in whom subclinical beriberi apparently precipitated premature heart failure of the congestive type There was characteristic reduction in heart size and prompt disappearance of venous stasis and edema when the patients were given an adequate diet and bed rest

The results were similar to those seen in absolute B_1 avitaminosis and suggest that pre existing disease particularly coronary insufficiency, may make the heart more vulnerable to B_1 deficiency

During the time this study has been in progress 23 additional patients have been treated for pellagra making a total of 48 endemic pellagrins who have been observed over varying

periods of time It is highly significant that in not a single instance has heart failure of the congestive type or angina pectoris developed This fact clearly indicates that pellagra does not affect the heart to a degree sufficient to impair its functional integrity

Conclusions

1 The clinical evidence and necropsy studies show that the hearts of endemic pellagrins are normal or subnormal in size

2 There are no characteristic electrocardiographic changes in endemic pellagra Those changes that do occur are invariably explained by vascular or toxic complications

3 Beriberi and pellagra have no comparable effect on the heart The difference is so absolute that one ventures the opinion that B_1 is not concerned with the pathogenesis of pellagra

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CHAPTER XXV

PROGNOSIS

The use of nicotinic acid in the treatment has reduced the death rate from pellagra very materially The prognosis of pellagra is good in the mild cases, approaching 100 per cent of recoveries provided (1) that the diagnosis is made early, and the patient is properly treated, (2) that the patient is financially able to carry out the prescribed dietary and hygienic regimen during treatment and for several years afterwards, (3) that the physician in charge of the case consistently and persistently encourages his patient and re educates him to live a simple, normal hygienic life after his recovery, and (4) that the recovered pellagrin is not exposed unduly to the direct rays of the sun for one or two years after his recovery

The prognosis of the uncomplicated moderately severe cases is good, provided they can be hospitalized or given careful treatment at home It is less favorable in cases in which because of ignorance, poverty and unfavorable home environment, the diet and medical treatment cannot be carried out satisfactorily

The death rate in the typhoid, or fulminating, type of pellagra is high, but fortunately that type, which was frequent in the early years of endemic pellagra, is now of rare occurrence It may be added that pellagra as it exists today is a very much milder disease than it was twenty or thirty years ago

The prognosis in pellagra due to alcoholism is not so favorable for the reason that the toxin (ethyl alcohol), the *primary* factor in causing the disease, usually has produced permanent changes in the liver and other organs of the body, particularly the nervous system, which preclude the possibility of the victim living many years even if he did not have pellagra

Various complications affect the mortality of pellagra It is of course hopeless for permanent recovery when secondary to inoperable carcinoma of the alimentary tract and in ulcerative colitis, but even in those cases the pellagra symptoms may be relieved or ameliorated by treatment

LeGrand Guerry, of Columbia, South Carolina, and Warren Hudson, of Hattiesburg, Mississippi, in papers on surgery in pellagra, stated that pellagrins rarely recover from serious operations. It therefore is important, except in emergencies, such as in acute appendicitis, to treat the pellagra before an operation is considered. Since pellagra has been reported as secondary to gall bladder disease by Turner and others the mortality from gall bladder surgery can be reduced by treating the pellagra before an operation is performed.

The mortality from pellagra is relatively high in the patients with severe psychoses, such as those treated in insane hospitals, but the fact that a patient is psychotic, or delirious, does not *preclude recovery*. Some of the most brilliant results which I have observed have been in pellagrins who, when first seen, were in a state of muttering delirium, or in profound melancholia.

The outlook is bad for a pellagrin with an intractable diarrhea that has existed for some time, but many of the patients with severe diarrhea will recover if they can be hospitalized, or treated properly at home.

The statistics of the high death rates in pellagra come largely from charity hospitals to which pellagrins go in the last stages of their malady. The statistics on pellagra as reported by boards of health are accurate probably 90 per cent, so far as the number of deaths are concerned, but they cannot give correct statistics as to the death rates from pellagra as related to the total number of cases of pellagra in any state.

The morbidity statistics of pellagra are valueless, for the reason that there are many cases of pellagra in which the patient gets well spontaneously without ever having consulted a physician and perhaps without ever knowing that he had pellagra. Many other chronic pellagrins are never sick enough to require medical attention, and some, not so many as the advocates of socialized medicine would have us believe, do not consult physicians because of poverty. Besides, physicians are prone to negligence in reporting their cases of pellagra.

The death rates from pellagra for a few years after it was found to be endemic in the South were very high, partly because it was not diagnosed until in the terminal stage in many cases,

and there can be little doubt that pellagra was a more virulent disease in the first reported outbreaks than it is at this time

The death rates from pellagra are higher among the negro than among the white population This cannot be explained entirely because of the alleged poverty of the negroes in the South In discussing the relatively high death rate of negroes, 33 7 per cent, as compared with 22 7 per cent of deaths among white patients, in their series Sydenstricker and Armstrong assert "Contrary to the general impression, the Southern negro lives well, and while his diet may be somewhat low in proteins of optimum biologic value it is rich in green vegetables of good vitamin B_2 (G) content Neglect of symptoms cannot be considered the cause, as the negro population from which these patients were drawn has been the object of almost paternal medical supervision for about a century, and medical advice is sought by them for the most trivial complaints"

C C Bass, of New Orleans, was one of the pioneers in studying pellagra Having been on the staff of the Charity Hospital, the largest teaching hospital in the South, he had a large experience in dealing with the disease His observations on the prognosis of pellagra, published in the *Southern Medical Journal* in 1912 are of interest in 1940, and what he said years ago applies in the main to the prognosis of pellagra at this time Nicotinic acid does not cure every case of pellagra Bass said

> How long must a patient be free from attacks of pellagra before he is safe from a recurrence of the symptoms? My observation would lead me to answer that if an attack can be avoided for twelve months or longer there is little danger of a return of the disease
>
> The so called typhoid pellagra seldom but occasionally gets well Pellagrous insanity is unfavorable but does not bar recovery Deep moist lesions are an unfavorable symptom Severe stomatitis indigestion or diarrhoea may produce death by starvation Other associated diseases render the prognosis of pellagra less favorable in a given case according to the prognosis of the particular disease

Suicidal and Homicidal Tendencies in Psychotic Pellagrins — In discussing prognosis in pellagra, the suicidal and homicidal tendencies in psychotic pellagrins should not be forgotten One of the three deaths from pellagra which I can recall in my private practice in thirty four years was by suicide It should be added that my pellagra patients, as most of my other patrons

in a consultation practice have been able to secure an adequate diet and be hospitalized when necessary

J W Babcock, the great South Carolina psychiatrist and pellagrologist, became interested in the medicolegal relations of pellagra many years ago Excerpts from a paper by him read before the Southern Medical Association twenty five years ago are worth reproducing in a chapter on Prognosis in Pellagra Babcock said

"It was doubtless a painful confession for the distinguished Landouzy to make when he said 'I have since been convinced that I once allowed to be executed for homicide a woman, who without doubt, had committed the deed during an attack of pellagra insanity' After his life long experience with the disease, and with the insane, Lombroso left the opinion that 'A common symptom of pellagra is the tendency to unpremeditated murder or suicide without the slightest cause The sight of water suggests drowning in the form of murder or suicide' Or as Marie says 'Suicides by drowning are numerous also by reason of a kind of motor automatism or instinctive impulsion similar to attacks in epileptics They do not know when they throw themselves into the water, and if they survive they cannot explain their attempt' This 'hydromania' of Strambio that is *the impulse of pellagrins to drown themselves, has been* discussed by all writers upon the disease since his time (circa 1785) Sorbets, *however takes a more comprehensive view of the subject* in asserting that 'nothing is more capricious or variable than pellagrous insanity Almost all pellagrins experience a special penchant to drown themselves although others perish by strangulation, or throw themselves from high places or according to Soler, into the fire' And he adds 'But it is not against themselves that pellagrins direct their insane acts under the influence of homicidal monomania they have other victims'

To this may be added the opinion of du Saulle 'Pellagrins, for example, who obey homicidal impulses which so frequently accompany their insanity have been condemned as murderers, and this with the consent of medical experts, or at least it is in accordance with the conclusions of their reports that these unjust sentences have been *pronounced*'

"Dr John Warnock Director of the Government Hospital for the Insane near Cairo reported in 1903 '*Fifty two patients suffering* from pellagrous insanity were admitted, of whom seven were criminal lunatics Delusions of persecution, of being put under a spell, or of being poisoned, etc are frequent mental symptoms of this malady, and it is therefore not surprising to find that five murders were committed by these patients before being sent to the asylum as criminal lunatics In 1902, also, two murders committed by men suffering from pellagra occurred to my knowledge These patients are very prone to suicide and to injure their children It is to be regretted that so many of them have to be sent back to their homes before recovery, especially as prolonged treatment would appear to cure a certain proportion of cases'

"Sandwith from his experience *with pellagra in Egypt*, has noted 'That many criminal lunatics, brought to the Cairo Asylum, are found

to be pellagrous, they have been arrested for some purposeless murder in consequence of delusions which they forgot and deny a few days after admission"

"I beg leave to submit a number of brief outlines of cases compiled from newspaper reports from many parts of the United States as well as from medical journals and selected from personal experience

"At Nashville Tennessee, in November 1911, J F W and wife filed a bill in the Chancery Court against H H R praying that an exchange of land for notes be declared void and that the transfer be set aside because the plaintiff was a sufferer from pellagra at the time of the transaction, and was not of sufficient soundness, mentally to protect him self in the trade

"Dr J J Watson of Columbia S C thinks a large proportion, probably 90 per cent of the pellagrins he has had under care in a general hospital prevaricate or fabricate Especially is this noticeable in their complaints against nurses for alleged omissions of the treatment ordered or for improperly carrying out the physician s directions Investigation has proven all such charges and suspicions to be without foundation Sometimes this mental attitude of pellagrins suggests the fabrication of Korsakoff s syndrome The hysterical character is also suggested It seems to arise either from amnesia or else from hallucinations It obviously is not due to a malicious desire to make mischief

My own opinion is that the several acts described in this paper have arisen from a mental condition due to the pellagrous intoxication which has either greatly modified or nullified individual responsibility

The cases cited here have occurred in eight states—North Carolina South Carolina, Georgia Tennessee, Alabama Mississippi Louisiana and Texas—and they necessarily must constitute but a small proportion of those actually occurring in this territory and in this country in the last three or four years and associated with pellagra since they have been compiled by a single student of the subject But collectively they demonstrate the variety of abnormal actions which have been attributable to the unknown poison of pellagra Furthermore these actions duplicate, in a general way, those reported by foreign observers"

SECTION VI

PROPHYLAXIS

CHAPTER XXVI

THE PREVENTION OF PELLAGRA

Since endemic pellagra is largely a rural and suburban disease its prophylaxis *consists in improving the economic* and sanitary conditions of those who live in pellagrous communities The solution of the food problem is largely educational, particularly in the rural districts, because there are few families so poor that they cannot have a milk cow, a few pigs, chickens eggs, and a garden Every man, woman and child in the Nation should be taught McCollum's dictum, i e the minimum nutritional needs of adults are one pint of milk one or two green vegetables, and one fresh fruit in addition to meat once a day and sufficient bread and butter to maintain body weight and to supply energy for the day's work This simple dietary *formula supplies all the vitamins, including nicotinic acid* needed to prevent pellagra, tuberculosis and many other diseases

The fact is that nutrition is the most important public health problem in America today Surveys show that at least 20 per cent of the population of the entire United States are under nourished, and it is probable that at least half the illness and as large a proportion of the deaths that occur in every state in the Union are among the one fifth of the population who suffer from *inanition Certainly the poorly nourished individ*ual is more susceptible to all diseases, including pulmonary tuberculosis, pneumonia, and other respiratory infections, the anxiety neurosis and insanity, the anemias, pellagra scurvy and beriberi, and every other disease due to dietary deficiency Likewise the death rates from all causes are highest among those who are malnourished

While the morbidity and mortality from *pellagra* and all other diseases can be reduced to a minimum when 100 per cent

of our population are properly nourished, all the burden of educating the public regarding the quality and quantity of food required to maintain health and prevent disease should not be borne by the city, county, state, and national health agencies. The major part of nutritional education programs should be carried on by the schools and colleges. It is also an important agricultural problem to be dealt with by the national, state, and county personnel of the various agricultural agencies. Agriculturalists should recognize that it is as essential to the prosperity of farmers to teach them to grow their own foods at home as it is to tell them how to prevent and cure hog cholera and how to combat the boll weevil and the insects that destroy cotton, corn, wheat, and other money crops. Newspapers, magazines, and farm weeklies in particular are glad to give space in campaigns of education to teach the public known facts regarding the simple principles of nutrition, if public health officials will provide the information in language that can be understood by the average man, woman, and child above the primary grades.

Enough has been said about pellagra and poverty as a public health problem; what is needed most in the Nation is for all classes of people in every state in the Union to be informed that health, happiness, prosperity, and longevity depend more upon eating the proper amounts of the right kinds of food than any other factor in personal hygiene. Each individual man, woman, and child should be taught that he has the privilege of being one of the units in the hundred and thirty million people who make up the greatest nation on earth, and that he can do his "bit" for his country, in peace as well as in war, if he will keep fit to work, and to fight if necessary, to enjoy his "inalienable rights to life, liberty, and the pursuit of happiness."

Sanitary Sewerage.—In considering measures to prevent pellagra, the investigations and conclusions of the Thompson Pellagra commission in South Carolina should not be forgotten. Siler, MacNeal, and Garrison found that the installation of a sanitary sewerage system in a cotton mill town stopped an epidemic of pellagra. They also found that in cotton mill villages in which there were no surface privies there was either no pellagra or only a few cases which originated in commu

nities where soil pollution occurs Many Southern physicians believe that the effective work done by the state departments of health and the county health units of the South has been a factor in reducing pellagra, while at the same time amebic dysentery, typhoid fever, uncinariasis, and other diseases, known to be due to soil pollution, have decreased

I do not believe that pellagra is due to a specific infection, but I do believe that there is sufficient evidence to prove that malaria, amebiasis, uncinariasis, and other chronic diseases due to infections are predisposing causes of nicotinic acid deficiency, *the essential factor in the production of pellagra* It, therefore, is evident that the eradication of the communicable diseases in the rural districts of the South will aid in reducing the incidence of, and the mortality from, endemic pellagra

Chronic Fatigue—It should not be forgotten that chronic fatigue is one of the predisposing causes of pellagra, and the farmer who toils from dawn until twilight without sufficient rest and recreation not only is shortening his life but he is predisposing or conditioning himself to develop pellagra, tuberculosis, pneumonia and other diseases There is reason to believe that one of the reasons why housewives in rural and suburban communities are more susceptible to pellagra than men and children is that chronic fatigue is a predisposing cause of pellagra

Mothers and housekeepers are the most overworked class of people in the world, particularly the wives of farmers, and it should be expected that the women who reside in pellagrous districts would become frequent victims of the disease They get up *before daylight, cook breakfast, and then awaken the men* of the farm They slave all day, often depriving themselves of food so that their husbands and children may have more to eat, and sometimes they wash dishes at night when the rest of the family are in bed asleep The deadly drudgery of many housewives and mothers never ends until they break down physically, or mentally, or until a kind Providence ends their lives of toil and worry Certainly a campaign of education to prevent pellagra should include teaching, by public health nurses, and home demonstration workers, to impress housewives that the care of their own bodies is as important as taking care of their husbands and children

The Southern people have the reputation of being "lazy," but today in the rural districts as well as in towns and cities of the South long hours and overwork kill hundreds of men and women to one who dies of pellagra Therefore, a campaign of education should be inaugurated to teach all classes of people, farmers and wage earners, and housewives in particular, the dangers of chronic fatigue It is not necessary to tell them that accumulated fatigue over months and years predisposes to pellagra, but to teach them that the joy of living comes from work well done, combined with sufficient rest relaxation and recreation

Toxins—The campaign of education to prevent pellagra should include instructions regarding thrift and economy When poor people have been taught that the amount of money they waste on tobacco, coffee, soft drinks, and alcoholic beverages will provide their families with nourishing food, there will be less pellagra This campaign should be conducted first among doctors, who as a class, are as ignorant of the harmfulness of the toxins, nicotine, caffeine, and ethyl alcohol as the illiterate person who spends more money for tobacco coffee soft drinks, beer, and whiskey than he does for food

The late Dr J H Searcy, a great psychiatrist, in an address on mental hygiene related an incident which goes to the heart of the pellagra problem He said that on one occasion he was in a country store on Saturday, when a poor woman with two children came in to buy supplies for the week She laid a silver dollar on the counter and called for two bottles of coca cola one of which she drank and the other she divided between the two children Then she said "Gimme a dime's worth of snuff, and a dime's worth of chewing tobacco and a nickel bag of tobacco for the old man, and fifteen cents' worth of coffee" Thus, Dr Searcy said "the poor ignorant woman had spent half her dollar for toxins, with which to poison herself and family, and with the remaining half dollar she bought meal, meat, syrup and sugar"

The campaign of education to prevent pellagra should include instruction regarding the harmfulness of the caffeine beverages, all forms of tobacco, beer, and whiskey The poor certainly should be taught that tobacco coffee, beer, and whiskey

nutrition Not only that, if the adults of the present generation will put into practice the knowledge of food values and vitamins that are available to them, they can greatly increase their efficiency and at the same time *add years to their lives*

"When one understands something of the facts regarding vitamins and food values, it requires no imagination to see that the widespread use by the American people of foods, deficient in the various chemical and nutrient properties, is leading to serious consequences

"Rickets, infantile scurvy, and digestive and nervous diseases are surely increasing among infants, and strong virile adults do not develop from defective children The diet of white flour and white meal, polished rice, potatoes, and sweets that is used by the great majority of Americans is deficient in many ways, and if the next generation is to be an improvement physically and mentally over the average men and women of today it is important to add to our dietaries more milk, more raw fruits and vegetables and more leafy green vegetables In other words, the greatest public health problem of today is to educate the public regarding the need of a cow, a garden and an orchard for every country home, with enough dairies, truck and fruit farms to supply the city dwellers with the milk, fruit and vegetables necessary to keep them healthy and efficient "

Sebrell on Foods Containing the Pellagra Preventive Factor—Sebrell, now in charge of pellagra prevention in the United States Public Health Service, in Reprint No 1632, published a table showing the pellagra preventive value of various foods Among those he lists as *good*, which he said "contained enough of the pellagra preventive factor (now believed to be nicotinic acid) to prevent the disease The most valuable class of foods in the prevention and treatment of pellagra" are the following beef, fresh and canned, chicken, haddock, liver, pork, dried, pork, shoulder lean, rabbit, buttermilk, collards, canned, kale, canned, and green peas

Sebrell lists the quantities of the foods and the quantities of yeast required to prevent pellagra Thus it requires approximately ten or twenty times as much by weight of turnip greens, meats, and fish as brewers' yeast to prevent pellagra It requires 30 Gm of brewers' yeast to prevent pellagra while it takes 1,200 Gm (one and one fifth quarts or five glasses) of buttermilk to have the same effect

It should be easy for the pellagrin or the man exposed to pellagra to drink five glasses of buttermilk a day Or, if he will drink one or two glasses of milk, eat meat once a day, and large servings of green vegetables once or twice a day, he will get the

needed quota of nicotinic acid Why use yeast in the prevention and treatment of pellagra when it is so easy to get cheap and good food that contains as much of the pellagra preventing factor?

McCollum on Foods as Best Source of Vitamins.—E. V. McCollum, of Johns Hopkins School of Hygiene, and the greatest expert on nutrition in the world, said regarding prevention of pellagra in 1918:

> "It is now commonly believed that the only effective means of preventing or curing pellagra is the adherence to a diet containing suitable amounts of milk, eggs and vegetables, especially green leafy vegetables."

As to sources of vitamin B, the following is excerpted from McCollum and Simmond's book:

> "Vitamin B is very abundant in many of our common foods, such as tubers and root vegetables, leafy vegetables, fruits, cereal grains such as wheat, oats, corn, etc., peas, beans and glandular organs of animals, such as liver and kidney. It is not found in any fats or oils of either animal or vegetable origin. Such manufactured products as white meat flour, degerminated corn meal, polished rice, starch, sugar, glucose, muscle meats and fats and oils of both animal and vegetable origin are either lacking in this substance or contain it in very inadequate amounts. It is especially abundant in green vegetables such as spinach, leaves of turnips or beets, radishes, water cress, lettuce and to a lesser extent in cabbage, collards and Brussels sprouts. It will be seen that the selection of a food supply so as to contain an abundance of the vitamin B is a simple matter. There is likely to be a deficiency of this substance in the diet only when it is more or less unwisely restricted to a few articles or is derived in great measure from a few manufactured products, together with lean meats.
>
> "*In the case of the vitamin B as with the vitamin A, the place to secure it is in wholesome natural foods and not in commercial preparations heralded as containing this substance in high concentration.*"

The Passing of the Yeast Fad.—While there is scientific basis for the use of yeast as a temporary source of nicotinic acid in the treatment of pellagra, there is not proof that its use in the prophylaxis and cure of the disease is more effective than the employment of a high protein diet rich in vitamins, and at the same time containing the proper proportions of carbohydrates, fats, and minerals required for normal nutrition. Years before yeast was propagandized as a remedy for pellagra, many physicians in the South had as low mortalities, and as high a per

centage of recoveries and permanent cures with their pellagra patients, as have ever been reported by the most enthusiastic advocates of yeast.

Enterprising yeast manufacturers have advertised their merchandise so successfully as a remedy for all the ills of mankind that it is said three fourths of this fungus produced commercially is now sold over the counter for therapeutic use by a gullible public. Producers of brewers' yeast have propagandized their product for use in preventing and curing pellagra to such an extent that pellagrins and pellagrophobiacs buy yeast without consulting a physician, and the public is forgetting the value of Goldberger's balanced diet in the prevention and cure of the disease.

If all the money that has been spent for yeast by the state and federal governments, and the Red Cross, added to that spent by victims of pellagra and pellagrophobiacs, had been used in providing good food for the poor in pellagrous districts, and in carrying out a campaign of education, teaching farmers to raise their own corn, wheat, vegetables, fruits, dairy cattle, hogs, chickens, eggs, and other food products at home, the endemic pellagra problem would be nearer to solution. Even if the money that has been spent in advertising yeast to physicians and to the public had been used in enlightening the public regarding the use of proper foods in preventing and curing pellagra, much more could have been accomplished than has been done by use of all the yeast that has been consumed by a gullible public.

I would estimate that for every cake of yeast that has benefited a pellagrin, a ton has been wasted in giving this fungus indiscriminately to people in pellagrous districts with the hope that "yeast will act like magic in curing and preventing pellagra." It can be stated without fear of contradiction that *yeast never cured a case of pellagra permanently without improvement in diet. It may be added also that yeast never prevented an outbreak of pellagra without a concurrent improvement in the food supply in pellagrous districts.*

The indiscriminate use of yeast to prevent pellagra cannot be justified by the present knowledge of nicotinic acid in its rela-

tion to the disease and by the results in the use of yeast as a prophylactic against pellagra

There are signs that the yeast fad is passing, and it is predicted that in another decade this fungus will be found only in brewery vats, in bakeries and in kitchens, places where it may be used rationally and to advantage in human economy

The Futility of Distributing Nicotinic Acid to Prevent Pellagra.—Nicotinic acid enthusiasts and enterprising manufacturers of nicotinic acid have begun a propaganda campaign to persuade the gullible element among public health officials and dispensers of philanthropy to substitute nicotinic acid for yeast for widespread distribution in areas in which epidemics of pellagra are said to be threatening Certainly there is no place in the United States in which the expenditure of public or philanthropic funds for the "hit and miss" distribution of nicotinic acid to prevent pellagra is justifiable

It also has been suggested that wholesale quantities of nicotinic acid be sent to war devastated areas in Europe I made investigations regarding food conditions and nutritional diseases in Europe following World War I Millions of Germans, Austrians and Italians were on the verge of starvation but I could find no pellagra in the areas which I visited, and not a cake of yeast was distributed in those countries

Scurvy, particularly in infants, was very prevalent among the undernourished inhabitants of Europe during, and after, World War I Why not distribute ascorbic acid to prevent scurvy in Poland, Finland, Norway, the Netherlands, Belgium, and France? Rickets likewise was prevalent in undernourished children in Europe during and after World War I, and no doubt it is a problem in the present devastated countries Why not distribute ergosterol to the starving people of Europe? No doubt riboflavin deficiency will be responsible for much disease and many deaths in war stricken Europe Why not send riboflavin to the undernourished millions in the countries devastated by the German war machine?

I believe that philanthropy to prevent pellagra scurvy, rickets, tuberculosis, and other diseases in which undernutrition is a factor in prostrated Europe may be administered best at the proper time by sending the war victims wholesome food,

containing nicotinic acid, riboflavin, ascorbic acid, ergosterol, and other vitamins essential to health and life

Wheeler on Food in the Prevention of Pellagra—Wheeler, associated with Goldberger, and whose name should be mentioned whenever Goldberger is praised, expressed in forceful language thoughts that have been in the minds of many thoughtful physicians who reside in the rural districts of the South, when he said

"There is a day dream with which I frequently indulge myself, that is the re creation of the old time rural homestead in the cotton belt with its cows, chickens, pigs, and a good garden Pellagra is practically never found under such conditions of life It can be safely said, I believe, that the reason it is not found is that it is not there To restore such conditions among our cotton farmers would carry us a long way toward the solution of the pellagra problem *The disintegration of this* sort of living appears to have had its beginning with the breaking up of the old plantation life in the South about the time of the Civil War, and it has become more and more pronounced since

"Since pellagra is principally a disease of the rural areas including the smaller rural industrial communities, it naturally and very *logically* follows that to be permanently successful we must strive to bring about such changes in farming practices as will adequately safeguard the food supply of the small or tenant cotton farmer, regardless of the size and quality of the cotton crop, or the amount of cash it may bring Boiled down this means diversified farming, including the production of more, and a wider variety of vegetables, meats and dairy products *for home consumption* *This is regarded as the most*, if not the only, certain and dependable means of insuring their regular use The cotton farmer must be induced to farm more for a living and less for immediate cash if his nutritional ills, which doubtless include more than the frank cases of pellagra observed, are completely and permanently *to disappear* *A greater and more* uniform production of the more essential foods will also mean a ready and more abundant source for the smaller and more isolated industrial communities "

The Physician's Duty in Pellagra Prophylaxis—Appropriately placed on the walls of the original library in the Johns Hopkins Hospital were a number of brass plaques on which were inscribed aphorisms, or proverbs, selected from the literature of various nations No doubt they were chosen by William Osler, who was a great philosopher, as well as the ablest physician of his time In the summer of 1900 while doing some work on malaria under the late William Sidney Thayer, then an instructor in Johns Hopkins Medical School, I was so impressed

with some of these aphorisms that I memorized them One in particular, of anonymous origin, but supposedly an East Indian proverb, impressed me It is quoted from memory

But Once

"We shall pass through this world but once
Therefore if there is any good that I can do
Or any kindness that I can show to any human being,
Let me do it now,
For I shall not pass this way again"

The physician's duty does not end with prescribing diets and medicines and the general care of his patient, he should never miss an opportunity to prevent other members of the same family from contracting the disease which he is treating in one, or more, members of the household This principle practiced by true physicians places the medicinal profession far above commercialism, and it makes the doctor a humanitarian, who considers public welfare before personal profit The history of the medical profession in the prevention of disease thrills with acts of heroism and Carlos Findley, Walter Reed, Gorgas Carter, Agramonte, Lazear, and Carroll are among the immortals because they risked their lives to eradicate yellow fever No less heroic is the country doctor, or the city specialist, who risks his life and gives his time to prevent his patients from acquiring endemic or epidemic diseases

It cannot be said that the doctor who treats pellagra risks his life any more so than when he treats malaria, amebiasis, and uncinariasis, but nevertheless he is "a hero in the strife," if, when he is called in to see a case of pellagra, he carefully studies the environment of his patient, and, finding that other members of the household are living on a faulty diet or that they have insufficient food, he instructs them regarding the necessity for eating sufficient nutritious food If there are open privies, or if the well is not properly protected, or if there are flies in the house, or other factors in the patient's environment conducive to spreading diseases due to soil pollution, he should warn the family of contracting diseases that frequently precede or complicate pellagra While there is not the slightest evidence that pellagra is transmitted by mosquitoes, if there are breeding places around the home, or if there is malaria in the

neighborhood, the pellagra patient should be kept under a mosquito net if the house cannot be screened

The physician should regard it as an important duty to report to his county, or city health officer, that he is treating a case of pellagra and request that an investigation of the cause of the disease should be made at once, and request also, if a public health nurse is available, that she be sent to the pellagrin's home to instruct the family regarding the diet and methods of preparing food, which will promote the general health of the family and prevent them from developing pellagra

If physicians who treat pellagra will cooperate with their local health authorities, and with local welfare agencies when necessary, in dealing with every case, they can aid in preventing *other cases* Certainly *physicians practicing* in localities in which pellagra is endemic should not let an opportunity pass to do their part in the effort to limit the ravages of pellagra

CHAPTER XXVII

PLAGUES FROM THE USE OF DEVITAMINIZED FOODS

The ten plagues of Egypt—the plague of blood, the plague of frogs, the plague of lice, the plague of flies, the plague of destroying all cattle, the plague of boils, the plague of hail, the plague of locusts, the plague of darkness and murder, and the plague of killing the first born, did not punish the recalcitrant Egyptian, as much as the inhabitants of this so called civilized world have been cursed in the last century through "man's inhumanity to men" in profiting by devitaminizing foods and substituting artificial vitaminless foods for natural nutrients

Beriberi.—The most striking illustration of a plague from devitaminizing food was in selling polished white rice to the Chinese, Japanese, and the East Indians, who subsist largely on rice

There are no records to show that beriberi was a scourge in Eastern Asia until about a hundred years ago when someone discovered that white rice would keep better than whole grain rice, and that it was profitable to polish rice in large quantities Because it was profitable to manufacture and sell white rice to the inhabitants of Eastern Asia and because the Chinese, Japanese, and East Indians were ignorant of the fact that white rice is deficient in a protective food substance, vitamin B_1 (thiamin) they stopped eating whole grain rice As a result hundreds of thousands of human beings died of a food deficiency disease known as beriberi Following the change from whole grain rice to polished white rice beriberi became a scourge in Japan about seventy five years ago Takaki's famous experiments with sailors in the Japanese Navy in 1880 proved that beriberi is a food deficiency disease By increasing the amount of meat and vegetables and adding condensed milk to the rations of Japanese sailors Takaki decreased the number of cases of beriberi on one ship from 169 cases among 276 sailors to 14 Takaki,

however, did not recognize the fact that beriberi is due to a deficiency of a protective food substance in the outer coatings of rice

Casimir Funk, Benefactor of Mankind—Casimir Funk, working in the Lister Institute in London in 1911, isolated the beriberi preventive factor from the polishings of white rice It contained a protein, an amine, and since this substance was necessary for the life of fowls and human beings, Funk coined the word "vitamine," from the Greek words, *vitas* meaning life and *amine*, a chemical constituent of proteins Funk found that yeast was rich in the beriberi preventive factor, and he isolated three different chemical compounds from yeast, including nicotinic acid No ruler of any nation and no military conqueror ever issued a proclamation of such importance to mankind as Casimir Funk's historic paper entitled "The Etiology of Deficiency Disease," published in 1912 In this epoch making document, Funk announced his belief that scurvy, beriberi, pellagra, rickets, and sprue are deficiency diseases

The rulers of Japan, China, and the rice eating countries in East India applied the knowledge acquired by Casimir Funk and others when they enacted and enforced laws against the sale of white rice, with the result that beriberi was reduced enormously within a decade There can be no doubt but that the plague of devitaminizing rice, thus causing beriberi, cost hundreds of thousands of lives There also cannot be any doubt but that in the last quarter of a century, since the use of devitaminized rice has been stopped, millions of Japanese, Chinese, and East Indians are living today who would have died had not the governments of those countries prohibited the importation, *manufacture, and sale of white rice*

The Plague of Pellagra and Other Food Deficiency Diseases in the United States—Plagues followed devitaminizing essential foods in the United States of America, and a large proportion of the people in the greatest nation on earth, from college presidents to illiterates, are today as ignorant of the fact that they are being starved by eating devitaminized white flour and white meal bread and white rice as were the "heathen Chinese" when they ate diets made up largely of white rice About a century ago the roller process of milling wheat and corn into

white flour and white meal was discovered When it was found profitable to manufacture and sell devitaminized flour and meal the American people began starving themselves by eating bread devoid of vitamins There are many thousands of people in the United States today who, while they do not have beriberi have various forms of neuritis and vague nervous disorders, because they do not get a sufficient quantity of vitamin B to be nourished properly There is no evidence to show that pellagra was endemic in the United States until devitaminized white corn meal came into general use among the poor people in the sections of the country in which corn bread is the principal article of food

White flour bread and white corn meal bread are not harmful in themselves and there is no danger in their use, when enough milk, vegetables and fruits rich in vitamin B are eaten to make up the deficit of vitamins in bread, but the poor cannot buy the other foods and since they subsist largely on devitaminized bread, they are prone to develop many food deficiency diseases

The manufacturers of white flour and white meal also prepare feed for chickens cattle, and swine They have learned that they must add vitamins to the food they sell for animals to produce healthy chickens, cattle, and hogs, but they continue to manufacture and sell devitaminized flour and meal for human beings Of course the manufacturers of white rice, white flour, and white meal do not realize that they are depriving millions of people of food elements necessary to maintain health and life, and they have persuaded themselves that there is no harm in devitaminizing food for human consumption The public as a whole is as ignorant as many of the white flour and white meal manufacturers are of the damage that is being done to the American people by the use of devitaminized foods

It should be said in defense of the manufacturers of white flour and white meal that they are meeting the demand of their patrons, who are not informed of the fact that they are consuming devitaminized food Some of the best men among my friends manufacture flour and meal by the roller process, and I know that they would prepare whole wheat flour and whole grain corn meal, if there were the demand for those products

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White flour bread and white corn meal bread are not harmful in themselves and there is no danger in their use, when enough milk, vegetables and fruits rich in vitamin B are eaten to make up the deficit of vitamins in bread, but the poor can not buy the other foods, and since they subsist largely on devitaminized bread, they are prone to develop many food deficiency diseases

The manufacturers of white flour and white meal also prepare feed for chickens, cattle, and swine They have learned that they must add vitamins to the food they sell for animals to produce healthy chickens cattle, and hogs, but they continue to manufacture and sell devitaminized flour and meal for human beings Of course the manufacturers of white rice, white flour, and white meal do not realize that they are depriving millions of people of food elements necessary to maintain health and life, and they have persuaded themselves that there is no harm in devitaminizing food for human consumption The public as a whole is as ignorant as many of the white flour and white meal manufacturers are of the damage that is being done to the American people by the use of devitaminized foods

It should be said in defense of the manufacturers of white flour and white meal that they are meeting the demand of their patron , who are not informed of the fact that they are consuming devitaminized food Some of the best men among my friends manufacture flour and meal by the roller process, and I know that they would prepare whole wheat flour and whole grain corn meal, if there were the demand for those products

It also should be said to the credit of certain flour millers, who have learned that the roller process of manufacturing flour removes the vitamins contained in the wheat germ, that they are trying to perfect a process of saving the wheat germ now wasted in milling, by shipping with each barrel of white flour a quantity sufficient which, when added to the flour, will make it approximately of the same vitamin content as a barrel of whole wheat flour

Flour manufacturers have begun to market wheat germ, a by product prepared by the gravity method from the residue in milling flour by the roller mill process The Nebraska Consolidated Mills Company of Omaha, Nebraska, has had animal assays of the thiamin content of their wheat germ It is said to contain 10 to 13 international units of B_1 per gram Since an adult requires from 500 to 600 international units of thiamin a day, it will be necessary to use from 4 to 6 heaping tablespoonfuls of this wheat germ a day to provide ample thiamin to prevent vitamin B_1 avitaminosis

Wheat germ, while not as rich as yeast in the pellagra preventive factor in vitamin B_1, is a good source of nicotinic acid Wheat germ may be added to white flour or white meal before cooking, or it may be added to cereals, milk, or to any other food It has a very palatable taste

Wheat germ is inexpensive, though not as cheap as it should be, since it is made from a waste product in the manufacture of flour, and it would seem that public health workers should recommend its use to the inhabitants of pellagra communities in which white corn meal is the principal article of food

The wheat weevil and various fungi will not live in white flour, but they thrive in the wheat germ, so that it should be purchased in quantities to last for only two or three weeks The wheat germ will keep indefinitely if stored in a refrigerator

The Hardin Bakeries in Mississippi and Alabama now add the wheat germ to the white flour they use in making loaf bread They are conducting a campaign of education to teach their patrons to use whole wheat bread, or bread containing the vitamins, formerly eliminated in manufacturing white flour They also are endeavoring to teach the population in the sections of Mississippi and Alabama which they serve regarding

the vitamin and caloric content of all foods, stressing the necessity of the daily consumption of three adequate, well balanced meals Other manufacturers of bread should serve their customers in a similar way "He profits most who serves best"

Progressive Legislation—The ideal method of stopping people from starving themselves by eating devitaminized bread would be to pass laws in every state in the Union and by the United States Government prohibiting the importation, manufacture, and sale of devitaminized flour, meal, and rice Before such a law can be passed and enforced the public should be taught the truth about the danger to health that follows *the use of devitaminized foods* *Public health officials should* join in such a campaign of education, because the number of cases of illness and the number of deaths from pellagra and other nutritional diseases will be reduced materially when the American people use whole wheat flour and whole grain corn meal in making their bread and substitute brown or whole grain rice for devitaminized white rice

If the state health departments of the states in which pellagra is endemic could secure legislation prohibiting the importation, manufacture, and sale of devitaminized white meal, and if the farmers could be taught to grind their own meal from home raised corn, it would be a long step towards reducing endemic pellagra to the irreducible minimum Before such progressive legislation can be enacted, all classes of people in the states affected should be taught to consume less corn bread and to eat more meat, vegetables, fruits, eggs and butter, and to drink more milk

Small Gristmills—Recently I had the privilege of discussing deficiency diseases which exist in the United States with Dr Haven Emerson, Professor of Preventive Medicine at Columbia University Dr Emerson regards the use of devitaminized foods as one of the most important public health problems of the present time Dr Emerson, practicing what he preaches, has a hand mill, with which he grinds wheat into whole grain flour, and he and his family eat delicious bread made from whole grains of selected wheat If every family of this nation possessed an inexpensive small mill for grinding selected wheat and corn into flour and meal for their personal use, the health

It also should be said to the credit of certain flour millers, who have learned that the roller process of manufacturing flour removes the vitamins contained in the wheat germ, that they are trying to perfect a process of saving the wheat germ now wasted in milling, by shipping with each barrel of white flour a quantity sufficient which, when added to the flour, will make it approximately of the same vitamin content as a barrel of whole wheat flour

Flour manufacturers have begun to market wheat germ, a by product prepared by the gravity method from the residue in milling flour by the roller mill process The Nebraska Consolidated Mills Company of Omaha, Nebraska, has had animal assays of the thiamin content of their wheat germ It is said to contain 10 to 13 international units of B_1 per gram Since an adult requires from 500 to 600 international units of thiamin a day, it will be necessary to use from 4 to 6 heaping tablespoonfuls of this wheat germ a day to provide ample thiamin to prevent vitamin B_1 avitaminosis

Wheat germ, while not as rich as yeast in the pellagra preventive factor in vitamin B_1, is a good source of nicotinic acid Wheat germ may be added to white flour or white meal before cooking, or it may be added to cereals, milk, or to any other food It has a very palatable taste

Wheat germ is inexpensive, though not as cheap as it should be, since it is made from a waste product in the manufacture of flour, and it would seem *that public health workers should* recommend its use to the inhabitants of pellagra communities in which white corn meal is the principal article of food

The wheat weevil and various fungi will not live in white flour, but they thrive in the wheat germ, so that it should be purchased in quantities to last for only two or three weeks The wheat germ will keep indefinitely if stored in a refrigerator

The Hardin Bakeries in Mississippi and Alabama now add the wheat germ to the white flour they use in making loaf bread They are conducting a campaign of education to teach their patrons to use whole wheat bread, or bread containing the vitamins, formerly eliminated in manufacturing white flour They also are endeavoring to teach the population in the sections of Mississippi and Alabama which they serve regarding

the vitamin and caloric content of all foods, stressing the necessity of the daily consumption of three adequate, well balanced meals. Other manufacturers of bread should serve their customers in a similar way. "He profits most who serves best."

Progressive Legislation.—The ideal method of stopping people from starving themselves by eating devitaminized bread would be to pass laws in every state in the Union, and by the United States Government prohibiting the importation, manufacture, and sale of devitaminized flour, meal, and rice. Before such a law can be passed and enforced the public should be taught the truth about the danger to health that follows the use of devitaminized foods. Public health officials should join in such a campaign of education, because the number of cases of illness and the number of deaths from pellagra and other nutritional diseases will be reduced materially when the American people use whole wheat flour and whole grain corn meal in making their bread and substitute brown or whole grain rice for devitaminized white rice.

If the state health departments of the states in which pellagra is endemic could secure legislation prohibiting the importation, manufacture, and sale of devitaminized white meal, and if the farmers could be taught to grind their own meal from home raised corn, it would be a long step towards reducing endemic pellagra to the irreducible minimum. Before such progressive legislation can be enacted, all classes of people in the states affected should be taught to consume less corn bread and to eat more meat, vegetables, fruits, eggs and butter, and to drink more milk.

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of all classes would be improved enormously It would be an excellent idea for every county health unit in the United States to own a small mill for the home grinding of wheat and corn, and use it to demonstrate how people may retain the vitamins in their food and at the same time have bread which has a better flavor than the breads made from devitaminized white flour and white meal

With rural electrification farmers may install, without great expense, a small mill which will grind the wheat and corn for themselves and neighbors, and have a surplus to sell to neighborhood stores Such small mills are being installed in many rural communities which have electricity available It is a hopeful sign for the future health of America that people are being educated to use wholesome food made at home instead of the devitaminized white flour and white meal manufactured in the West and shipped all over the country I do not single out Western flour and meal manufacturers as being the only offenders in depreciating the health of the American people by selling devitaminized foods, flour and meal manufactured by the roller process in Georgia and other southern states are just as devoid of vitamins as if manufactured in Nebraska

The United States Government should apply the pure food laws to control the sale of devitaminized flour and meal by requiring that each sack or package of flour and meal should be labeled to warn the consumer that it is devoid of vitamins essential to health and life The United States pure food laws require that the label on each package of artificial butter must carry a statement that it is made from fats other than that derived from cow's milk If the pure food law would protect the public from the food deficiencies which follow the use of vitaminless butter, it surely should apply it to protect the consumers of bread, "the staff of life," from the deficiency diseases which follow the use of this devitaminized food, the principal article in the diet of millions of Americans

Devitaminized Butter—One of the great discoveries in the field of nutrition was by E V McCollum in 1909 and 1910 when he and his associates proved that milk contains fat soluble protective substances, now known as vitamins A and D It also was proved that a substitute for butter, oleomargarine, then

on the market was devoid of the fat soluble substances in butter which protect animals and human beings from eye diseases, general infections, and rickets, but that did not stop enterprising manufacturers of artificial butter from selling their products This substitution of artificial foods devoid of vitamins for natural nutrients rich in essential elements has brought on the plague of deficiency diseases due to lack of vitamins A and D Butter made from milk fat is rich in vitamins A and D, but artificial butter, oleomargarine and margarine butters, sold under various trade names, made from cottonseed oil, devoid of vitamins, looks, smells and tastes like genuine butter It has been found so profitable to manufacture and sell artificial butter that today a large proportion of the butter sold in the United States is made from cottonseed oil

While it has not been proved that vitamin A protects against tuberculosis and many other infections, there can be little doubt but that such is a fact The reduction of tuberculosis by 75 per cent in the last half century has been pari passu with an increase in milk consumption of several hundred per cent That the growing use of artificial butter is a menace to the health of the people who use it will not be denied by any one who knows anything of nutrition

Ever since the days of Dr Harvey W Wyley and Theodore Roosevelt, efforts to stop the manufacture and sale of oleomargarine and similar products have been made but Southern senators and congressmen rise up in indignation at the effort "to cripple the farmers who raise cotton" and they have been able to prevent national legislation on the subject I am an Alabamian but I would like to go on record as favoring legislation by states, and the United States Government, prohibiting the manufacture and sale of butter made from cottonseed oil or anything else except milk It is true that the manufacturers now claim that they irradiate their margarine butter, thus adding vitamin D, but do they?

Wisconsin Laws—The state of Wisconsin recently passed a law, taxing artificial butters so high that it is cheaper for consumers in that state to buy butter manufactured by Wisconsin creameries than to buy margarine butters manufactured in New York and Chicago from cottonseed oil made in the South The

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people of Wisconsin do not consider the question of health so much as they consider profits just as the people of New York and Alabama "howl when their pocket books are hit" Although I do not believe in state tariffs, or reprisal laws, I am heartily in favor of the Wisconsin law taxing artificial butter out of existence I think there should be a national law prohibiting the manufacture and sale of artificial butter made from cottonseed or anything else, but from a different motive than that of the Wisconsin legislators Such a law would promote the health of the general public, and the question of profits for someone should not be considered

Health officials not only should use the weight of their official positions to secure legislation to prevent the importation, manufacture, and sale of butter substitutes, but they should enter into active campaigns of education to teach farmers, whether sharecroppers or plantation owners, to keep enough milk cows to provide every member of their families and every laborer employed by them, with at least a pint of milk a day and a quart of milk a day for every child in their families Farmers also should be taught that dairying is an important source of income for them The figures are not available but dairying in Wisconsin has made the farmers of that state independent economically, and they do not have pellagra

McCollum and Simmonds said "The most important improvement in the nutrition of peoples has come from an increase in the consumption of milk and milk products," and it has been noted by a number of observers that people who consume plenty of milk, butter, and cheese do not develop endemic pellagra If a person will drink a pint of milk a day, even though he consumes large quantities of devitaminized corn bread, he will be getting sufficient vitamins to protect him from pellagra It also is a fact that the farmer who is thrifty enough to have a cow is likely to raise enough of a variety of meat and vegetables to keep himself and family well nourished

Public health officials should work unceasingly to deliver their people from the plagues that come from devitaminizing foods There is opportunity to reduce the morbidity and mortality rates in every state in the Union very materially by teaching the public the known facts regarding devitaminized and natural

foods An old prophet said "My people perish for lack of knowledge" Christ said "Ye shall know the truth, and the truth shall make you free" Health officials have been the prophets who saved their people from the ravages of yellow fever, malaria, typhoid fever, tuberculosis, and many other diseases, and now they should have the courage and the vision to undertake the task of driving from the United States of America the plague of food deficiency diseases due to the almost universal use of devitaminized foods

Home Raised Corn and Wheat—Farmers should be taught to raise and take care of their own corn and wheat and have it ground in neighboring mills as needed White meal and white flour are deficient in all the six, or more, component parts of vitamin B, and there are many students of the pellagra problem who have not been convinced that the toxins formed in fermenting grain, corn in particular, cannot be among the etiologic factors in the production of pellagra Italian pellagrologists point to the reduction in the consumption of polenta (corn meal mush) and the other corn products in Italy as being pari passu *with the decrease in pellagra Mussolini is furnishing Italian* peasants with seed wheat and rye to use in raising food crops instead of corn, in the hope of eradicating pellagra from Italy

Improvement in the general economic condition of the entire population of the states in which pellagra prevails will help solve the problem That means living wages for laborers and good prices for farm products

Italian Experience—The fact that in all the countries of southern Europe in which pellagra prevails, corn bread, or corn meal mush (polenta), is the most important article of diet, while in European countries in which no corn products are eaten pellagra is not endemic, has led to the belief for more than a century that a toxin in spoiled corn is the cause of the disease Proof that such was a fact, was not forthcoming, however, until in 1869 when Cesare Lombroso, the great Italian physician and criminologist, Professor of Forensic Medicine and Psychiatry in the University of Turin, made experimental studies which left no doubt in the minds of European physicians that a toxin ("pellagrazein") formed in moldy maize is the cause of pellagra Lombroso convinced his European con

freres so thoroughly that a toxin found in spoiled maize and other cereal grains was the cause of pellagra that they still adhere to that theory Lombroso's experimental studies in working out the physiologic actions of the toxins derived from bad maize and his production of pellagra like symptoms in animals, by the continued use of *those toxins, are fine example of thorough* scientific investigation on pellagra, and his conclusions cannot be disregarded in considering toxins formed in moldy meal and other corn products as possible factors in the etiology of pellagra

In Italy today the opinion prevails that chronic intoxication from toxins produced in moldy corn is the cause of pellagra, and Mussolini's dream of eradicating pellagra from Italy is based largely upon the elimination of corn products from the diets of the Italian peasants Mussolini is said to have issued edicts against raising corn in Italy, and his government is furnishing the agrarian population of his domain with wheat and barley to substitute for maize as food crops

If Italian statistics can be considered reliable, it appears that Mussolini is having greater success in Italy in eradicating pellagra by *limiting the use of corn products as a food by Italian* peasants, than we have had in the United States working on the basis that food deficiency is the sole cause of the disease Levy, of Houston, Texas, in discussing pellagra at a meeting of the Southern Medical Association, said "*In Italy, under the imperialistic* fascist rule of Mussolini, we find that in 1928 the *death rate from pellagra had declined to* 0 2 *per* 100,000 from a previous high in 1900 of 10 7 " While investigating food conditions and nutritional diseases *in Italy in 1919, I endeavored* to secure statistics on pellagra, but was informed by government officials in Rome that they had no records of value regarding the number of cases of pellagra in Italy All the Italian physicians agreed, *however, that pellagra was becoming a rare* disease in Italy

I would conclude that in our present state of knowledge regarding the etiology of pellagra it would be wise to eliminate all roller mill *process corn products from the diet of pellagrins* It also would seem wise for the inhabitants of states in which

pellagra exists and in which corn products are the principal source of food, to substitute breads made from wheat, barley, and rye for corn meal products, or to use whole grain corn bread and discontinue the use of devitaminized white corn meal

French Experience—The Southern states, the corn bread region, and the section of the United States in which endemic pellagra is a problem, should profit by the experience of the French Half a century ago when pellagra threatened to become a scourge in southern France, Roussel, a great physician, convinced of the soundness of Lombroso's theory, persuaded the French government to make it unlawful to plant corn in France Wheat, barley, and rye were substituted for corn, and in a few years pellagra disappeared in that country, and even in the food shortage during World War I, there was no pellagra in France I spent ten months as a medical officer in France during World War I and could find no one who had seen a case of pellagra During World War I the United States Government sent quantities of corn meal to France, but the French refused to use it, preferring to eat their coarse black barley bread, or none at all, than to run the risk of having pellagra from eating corn products

The conception of toxins as predisposing causes of pellagra by producing nicotinic acid deficiency correlates the viewpoints that the use of musty meal and other spoiled corn products and avitaminosis both play a part in the production of endemic pellagra I disclaim any intention of reviving the corn toxin theory of pellagra, except as one of the predisposing factors in its production I merely insist that a careful study of the literature on the relation of corn toxins to pellagra will convince the unprejudiced student of the problem that fungi growing in corn meal may play a part in the production of endemic pellagra I believe, however, that the avitaminosis resulting from the use of western ground, devitaminized, white corn meal, as the principal article of food, is a more important etiologic factor in endemic pellagra than the toxins elaborated by fungi growing in musty meal

McCarrison on Devitaminized Foods and Deficiency Diseases in Civilized Man—Perhaps the one most important article ever

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published on the relation of food deficiency to gastrointestinal and other abdominal diseases is the Robert McCarrison Mellon lecture delivered before the Society of Biological Research, University of Pittsburgh, November 18, 1921. The facts which McCarrison presented apply equally in the relation of vitamin deficiency diets to pellagra. In this address McCarrison estimated that probably 25 per cent of the diseases of civilized man are of gastrointestinal origin due to dietary deficiencies resulting from the use of "preserved, purified, polished, pickled and canned foods." McCarrison also presents experimental proof of the production of abdominal diseases by the use of devitamized foods. He said that in one way or another "by desiccation, by chemicals, by heating, by freezing and thawing, by oxidation and decomposition, by milling and polishing, man applies the principles of his civilization—the elimination of the natural and the substitution of the artificial—to the food he eats and the fluid he drinks. With such skill does he do so that he often converts his food into a 'dead' fuel mass, devoid of those vitamins which are to it as the magneto's spark is to the fuel mixture of a petrol driven engine."

McCarrison proved that by means of faulty food, (1) diarrhea, (2) dysentery, (3) dyspepsia and gastric dilatation, (4) gastric and duodenal ulcer, (5) intussusception, (6) colitis, and (7) failure of colonic function can be produced experimentally. He said that he had seen amebic dysentery arise in deficiently fed wild monkeys, while other well fed monkeys escaped the disease, although subjected to the same risks of infection. In this instance, malnutrition had enabled the specific organism to implant itself in the tissues of the bowel.

In contrast to the frequency of abdominal diseases in civilized man McCarrison observed the relative infrequency of such disorders among the primitive people of a remote part of the Himalayas. McCarrison concluded that "imperfect nutrition prepares the soil of the body for the rank growth of bacterial agents", and he stressed the fact that "good foods—milk, eggs, grains, fruit and vegetables—no sugar—no alcohol—is a protection against nutritional diseases." He said that he was "in accord with Hindhede—that the two chief causes of disease and death are food and drink."

McCarrison did not mention that pellagra is a result of the use of devitaminized foods by civilized man, because endemic pellagra is not a problem in England or in the Himalayas, but the use of milk, eggs natural grains, fruits, and vegetables which he advised in the prevention of abdominal diseases is the best method of preventing endemic pellagra

Taboo Devitaminized Foods—The use of devitaminized foods opened up Pandora's box of human ills, and pellagra beriberi scurvy, tuberculosis, and all other infectious diseases, to which diets deficient in vitamins predispose, were turned loose to destroy the poor and ignorant classes of all nations All that is necessary to prevent the diseases caused by eating of what McCarrison called "dead" foods is to apply our present knowledge regarding vitamins This means the taboo of white flour, white meal, white rice, and white sugar and other foods which have been devitaminized by civilized man In other words, every intelligent man, woman, and child should eat breads made only from freshly ground whole wheat flour and freshly ground, whole corn meal White rice, white sugar products and butter substitutes should be discarded from the diets of all classes, and civilized people should go back to eating what McCarrison called "natural foods" which protected their ancestors from pellagra, beriberi, scurvy, and many other diseases in which a deficient diet is a predisposing factor

The flour, meal, and rice manufacturers will supply freshly ground whole wheat flour, whole grain corn meal, and whole grain rice when there is no longer a demand for their devitaminized products Physicians who are informed of the dangers from eating devitaminized foods should lead in a campaign of education to teach the public the known facts regarding the simple principles of nutrition They also may set a good example and promote the health efficiency and longevity of themselves and their families if they will stop using white flour, white meal, and white rice in their homes and substitute the better flavored and more wholesome, whole grain, cereal products Likewise public health officials should join in the crusade to teach healthful eating habits to their constituents It is important particularly to carry the fight against the plagues from eating devitaminized foods to the schools, espe

cially in the rural districts Intelligent eating not only will prevent pellagra, but it will increase the well being and prosperity in many localities in which food deficiency diseases should not exist

Starving Americans—It is true that the use of the "dead," devitaminized, white cereal products is not deleterious to health, provided that one will eat an abundance of vegetables and fruits, but the fact remains that not one person in a hundred who uses bread made from flour and meal manufactured by the roller mill process will get sufficient quantities of vitamin B for perfect nutrition

A recent survey showed that more than 20 per cent of the population of the United States are in a state of demonstrable undernutrition The probabilities are that there are not 20 per cent of the population of the United States who are properly nourished, and the starving ones are in the millionaire class, as well as among the ignorant and poverty stricken

Illustrating the starvation among the upper classes and the results from eating high carbohydrate, vitaminless diets, two instances may be mentioned En route to and from Washington, I had meals with two men who had been very successful in business Both were rated as millionaires Both were decidedly obese They had the opportunity in the dining car of ordering what they wanted, and no doubt ate the foods which they were accustomed to eating at home One ate several slices of white bread, ham and eggs, white cakes, 3 or 4 pats of butter and syrup, and at least six lumps of sugar in two cups of coffee with cream, for breakfast He now has diabetes The other who was complaining of back pains, neuritis of the back muscles, said that he was on a diet, and his evening meal consisted of several slices of white bread, fat roast beef, ice cream, and coffee with several lumps of sugar Both men were living on high carbohydrate, vitamin deficient diets, and now they are paying the penalty of overeating devitaminized foods "A man may starve with a stomach full of food"

There are millions of prosperous families in the United States who are obese but are vitamin starved on diets consisting largely of white bread, white rice, white potatoes, and white sugar products, such as desserts, candies, soft drink and, or, alcoholic

beverages They look fat and prosperous at forty, but they have inordinately high mortality rates after fifty from the degenerative diseases Some of them develop pellagra, and a very large proportion of them suffer from the neuritides, pains in the back and limbs what some call the infirmities of age, but which are due largely to diets deficient in vitamin B

The tragedies which follow the use of "dead," devitaminized foods come earlier in life among the poor, who are compelled from infancy to the end of their miserable lives to subsist on Western ground white corn meal bread, syrup and fat meat, and a few vegetables in the spring and summer They develop pellagra and tuberculosis and are even shorter lived than their brothers and sisters in the starving millionaire class, who get more milk, fruit and vegetables but not enough vitamin B to be properly nourished

It is evident from a study of the food habits of the American people that the taboo of "dead," devitaminized white flour, white corn meal, white rice, and white sugar products not only will reduce the incidence of endemic pellagra, but will add enormously to the health, efficiency, and longevity of millions, both rich and poor, who though living in a land of plenty are existing in varying degrees of starvation

CHAPTER XXVIII

PELLAGRA AND SOUTHERN PROSPERITY

Misguided Publicity.—The South has received much unfavorable publicity because of newspaper and magazine discussions of the pellagra problem. Zealots of food deficiency as the sole cause of pellagra in their efforts to mold public opinion to the need of improving economic conditions in rural districts of the Southern states in which pellagra prevails but is not a serious problem, have overshot their mark, and have left the impression that the *entire* South is backward and poverty stricken. They have exaggerated the seriousness of pellagra as a disease, and the extent of its ravages, by lurid descriptions of the symptoms and sufferings of the victims by calling it the "red death," and the "scourge," or the "plague" of the South.

No one denies that there is too much poverty and more pellagra than should exist in the South, and since in recent years statistics show that in proportion to population there are five times as many indigent in proportion to population receiving government aid in New York, Pennsylvania, and Ohio as in Alabama and other Southern states, it is evident that *all* the poverty does not exist in the states in which pellagra prevails. President Roosevelt speaks of the South as "the Nation's number one economic problem," yet statistics show that approximately five times as much Government money is being spent per capita for relief agencies in the *Northern* and *Eastern* states than in the Southern states.

The propaganda that pellagra is a disease which exists only among the ignorant and poverty-stricken "sharecroppers" of the South has been going on for a long time. In 1921 when I was editor of the *Southern Medical Journal*, there was so *much* pellagra publicity which was unfair to the South that I felt called upon to write the following editorial:

"The Pellagra Scare. A Gross Injustice to the South.

"The South has suffered much and long from *the reputation of being* unhealthful. There can be no question that many thousands of the

millions who have migrated from the North and Middle West to the Northwest and to Canada within the last few decades would have come South had it not been for the fear of yellow fever, malaria, hookworm and other tropical diseases This reputation of being a hot bed of disease has interfered very materially with the agricultural development of the most fertile lands in the United States and it has prevented many industries from locating in the favored South

"Yellow fever having been driven forever from the Gulf and Atlantic ports and malaria and hookworm having been eradicated in some, and greatly reduced, in the other Southern States, there has been the hope that many white farmers now living on the high priced lands of other sections of the country could be induced to take advantage of the opportunity to buy and cultivate the cheap and fertile lands of the South There is now the particular need for laborers to take the place of the hundreds of thousands of negroes who were lured from the farms of the South by the high wages in the industrial centers of the North during the World War and plans have been made in many Southern States to advertise in the North and West the opportunities that are open in the agricultural districts of the South with the hope of attracting white farmers from less favored sections of the country

The hope of inducing white laborers and farmers to come South has been rudely shattered by press dispatches that go to every paper in the United States and all over the world to the effect that the South is suffering from famine and that the starving millions are being attacked by the plague of pellagra a disease that results from starvation "

Unfavorable Advertising for the South —There can be no doubt of the sincerity of President Harding in his desire to help the South There is also no question that Surgeon General Cumming of the United States Public Health Service is honest in his effort to prevent the spread of pellagra in the South No one doubts Goldberger s honesty of purpose even though many do not accept his conclusions regarding the etiology of pellagra Therefore all those who have been responsible for the slander that the South is famine and plague stricken have been sincere but it will take years to undo the harm that the Southern States have suffered from such unfavorable advertising

The vigorous denial by the Southern health officers that famine exists and that pellagra is increasing or that it is prevalent to an alarming extent anywhere in the South will help to dispel the slander, but there should be a systematic effort to give to other sections of the country the facts regarding the health conditions in the South If the good people in the North and West knew that there are less than 10 000 deaths a year from pellagra among the 35 000 000 people living in an area of more than 1 000 000 square miles they would realize that pellagra is a comparatively rare disease in the South If they knew that there is not the slightest chance for another epidemic of yellow fever in any Gulf port and that malaria and hookworm are negligible diseases in all but a few localities in the South, and that the death rates of the whites in the North are higher than the death rates among the whites in the South many of them would move their families to the South where cheap lands fertile soil and balmy climate offer the greatest advantages to the farmer

If these facts were known in New England the cotton mills would come to the cotton fields and if they were known in other sections of the country our mineral and other industrial resources would be developed in a way that would amaze the world

"*The South's Opportunity*.—It is to be hoped that the good which is said to come out of evil will in this case result in the well directed effort to teach the people of other sections of the country that men, women and children can enjoy as good health, and do more work and make more money, in the balmy climate of the South than they can in any other section of the country General Gorgas proved in Cuba and on the Canal Zone that the white man can live and accomplish as much in the tropics as in colder climates He predicted that with the elimination of tropical diseases the future centers of industry and population would move to the tropics Agricultural and industrial development must first come to the temperate zone and these and many other blessings will come to the South when the living conditions here are known to the millions now living in less favored climates

"Another lesson that may be learned from the good intentions of misguided men is that we should 'keep our house in order' Goldberger's propaganda will be helpful to the South if our health authorities can be made to realize that malnutrition is the great predisposing cause of many diseases, including pellagra and tuberculosis A campaign of education for every family to own a milk cow and have a garden will help reduce the death rate The people of the South also should continue the fight on malaria and hookworm until they have been entirely eradicated

"This unfavorable advertising also should make physicians realize the importance of reporting the deaths births and diseases that occur in their practice When all the Southern States are in the 'registration area' when no one can doubt our vital and mortuary statistics, it will be a long step toward overcoming the deep rooted conviction in the minds of the people of the North, East and West that the South is unhealthful The progress of public health work in the South during the past two decades has been wonderful Our health authorities deserve and should continue to receive the cooperation of the public in the great constructive work that they are doing for the up building of the South"

Nineteen years have elapsed since this editorial was written, during which time the public health departments of the Southern states have been developed until they are admittedly superior to those of other sections of the country For instance, Alabama is the only state in the Union which has full time county health units, with physicians as health officers in every county in the state Every Southern state is now in the registration area of the Division of Vital and Mortuary Statistics in the Bureau of the United States Census, and the statistics of the number of deaths from pellagra in each state may be regarded

as at least 90 per cent accurate United States Census Bureau statistics show that the number of deaths from pellagra was reduced more than 50 per cent in eight years In 1929 there were 7,358 deaths from pellagra in the thirteen Southern states, and in 1936 the number had been reduced to 3,401 Statistics show that pellagra exists in every state in the Union until now it is a national problem There were 87 deaths from pellagra in California in 1936 and only 88 deaths from "the red death" in Kentucky in the same year Yet the uncorrected statements that "pellagra is the scourge of the South" continue to appear in the newspapers, magazines, and books by writers from other sections of the country

Many instances may be cited in which the South has been slandered by misinformed writers with good intentions

A New York Science Editor on Pellagra—In the year 1939, the science editor of a chain of newspapers with a total circulation of several millions, who has a vivid imagination but who evidently never saw a case of pellagra in his life, sat in his New York office and ground out a half page article with the screeching headline "Red Death—Pellagra" The following excerpts from the several columns of misinformation contained in this article show the author's ignorance of pellagra, and demonstrate his inexcusable lack of information regarding a great section of the United States

"Over the poverty stricken portions of the South there hangs the fearsome specter of the red death—pellagra How horrible the disease is only those who have seen it know

"It begins with a red rash that covers hands and face The victim grows gaunt and thin Terrible sores develop in the mouth so that it is impossible to eat

"The Sunshine, man s greatest friend becomes a curse, for the ultra violet light of the sun irritates the rash and makes it worse Finally the disease attacks the mind so that, when death arrives at last, it finds a half living sack of skin and bones from which reason has already fled

' But there is far less pellagra than there was once Medical men today know how to treat and even prevent pellagra That there is any pellagra at all is a direct challenge to the whole nation For the means are at hand for making the red death of the South a memory of the past like the black death that swept over Europe in the Middle Ages "

This author's comparison of pellagra in the South to the ' black death that swept over Europe in the Middle Ages" is

the vilest kind of slander Pellagra never has been, is not now, and never will be a "scourge of the South", but the millions residing in the North, East, and West, who read this calamitous and misleading description of the symptoms and course of pellagra, which he says *prevails in the* "poverty-stricken portions of the South," will believe that a person risks his life to visit, or to live, in the South

A Litterateur's Lack of Intellectual Honesty—An author, who has dramatized medical history in several popular books and in a series of radio broadcasts, is one of the worst offenders in spreading misinformation regarding the history and ravages of pellagra in the South He is a historian, who formulates startling statements in order to make money with his facile pen, or typewriter He certainly does not allow the truth to interfere with the reader's interest in his dramatization of medical history

This author's chapter on pellagra in one of his books, and his radio broadcast over a national hook up on the history of pellagra, contained many misleading misstatements A young matron from Mississippi, now living in Evanston Illinois, after reading this author's chapter on pellagra, in which he described the ravages of pellagra in insane asylums and orphanages in the South and among the ignorant and half starved sharecroppers in the rural districts in the Southern states, said that she was ashamed to admit to her friends, who had read the book, that she was from the South It is amazing that a man who pretends to write medical history would offend probably 25 per cent of his readers by libeling American citizens who make up more than one fourth of the population of the United States

Malaria Slander—This author, who ought to know better, in an article which was reviewed recently in the most widely read magazine in the United States said "Malaria, which kills 3,000 000 beings yearly in an unending world wide massacre, is not even beginning to be conquered in the South In the United States, it kills thousands of our people every year, it rots the blood of millions more, draining their energy so that they're less than half alive It does more to wreck development and the prosperity of the rural South than all other diseases put together"

A more inexcusable misstatement of facts has never been published than the effort to discredit the 35,000,000 people who live in the South. The statement that "malaria rots the blood of millions" in the South is literary rot, and is without foundation of fact. It is true that forty years ago malaria was a serious problem in the South, but after William Crawford Gorgas, an Alabamian, and Henry R. Carter, a Virginian, applied the knowledge that malaria and yellow fever are transmitted by mosquitoes in the sanitation of Cuba and the Canal Zone, health authorities in all the Southern states have done a remarkably fine job of preventing malaria, and no cases of yellow fever have been found in the South since 1905.

The author of this slander is just forty years from the facts when he says that "malaria is not even beginning to be conquered in the South." Following the epoch making work of Walter Reed, a Virginian, in proving Carlos Findlay's theory that yellow fever is transmitted by a mosquito, and Charles Wardell Stiles' proof that hookworm prevailed extensively in the South in the late nineties, the South became conscious of the fact that tropical diseases were a menace not only to the health and lives of people residing in rural districts but that a bad health record was affecting the prosperity of the entire South. The once dreaded yellow fever has been eradicated from the Gulf states, and the South has almost conquered malaria, as it has hookworm and other tropical diseases. In the year 1936 there were only four deaths from hookworm among the 2,846,485 inhabitants of Alabama.

Keeping the Record Straight.—Just to keep the record straight, why is it that more people in proportion to population die every year in New York and Pennsylvania than succumb to the "grim reaper" in Alabama? It is admitted that in the year 1937, in Alabama with a population of 2,846,485 living in an area of 50,000 square miles, out of the total number of deaths 31,175, a low rate of 11 per thousand, there were 306 deaths from pellagra and 345 deaths from malaria. Thus it will be seen that pellagra accounts for less than 1 per cent of the total number of deaths in Alabama, and that malaria causes a little in excess of 1 per cent of the deaths in one state of the "deep South." In other words, in Alabama, a typical Southern

state, in the year 1937 only 7 whites and 17 negroes out of every 100,000 population died from pellagra, and in the year 1936 only 5 urban whites and 10 urban negroes, and 10 rural whites and 23 rural negroes per 100,000 population died of malaria in Alabama

And it is a fact that Alabama is a safer place in which to live than New York or Pennsylvania According to statistics compiled by Dublin and Latka (*Length of Life,* p 87, Ronald Press Co, New York), the average child born in Alabama may expect to live 59 37 years, while the average child born in New York can expect to live only 57 84 years, and the still less fortunate average child born in Pennsylvania has a life expectancy of only 57 68 years If pellagra and malaria are "scourges" in the South, why is it that the average individual in Alabama lives longer than the average person in New York or Pennsylvania?

Omitting the inordinately high negro death rate in the South, the white death rate in the Southern states is considerably less than that of the whites in Northern, Eastern, or Western states For instance, in Alabama with a white population of 1,835,478, only 2 2 per cent of which are foreign born stock, and less than 1 per cent foreign born white, the total number of white deaths *amounted to 16,959, a death rate of only 9 2 per 1,000,* while among our negro population of 1,011,007, there were 14,238 deaths, a negro death rate of 14 2 per 1,000

Solving the Pellagra Problem—While I deplore the misstatements of the facts regarding pellagra and malaria, I would not withhold from the public the truth pertaining to every phase of any public health problem Conditions cannot be corrected until the public is informed of the facts as they exist The public certainly should known the truth regarding pellagra, though it has ceased to be a major public health problem in the South, and in order to prevent pellagraphobia, state health departments should publish the exact statistics of the number of deaths from pellagra which occur in each state in the Union The public also should be informed that with the use of nicotinic acid, liver and liver extracts, and an adequate diet primary, or uncomplicated, pellagra can be cured in 99 out of every 100 cases In addition, the campaign of education should be continued to improve the economic conditions in the districts in

which pellagra exists, as well as in every other part of the United States, until each man, woman, and child in every station of life can have three well balanced meals a day. When that is accomplished the incidence of pellagra, tuberculosis, the anemias, and other diseases in which impaired nutrition is a predisposing factor will be reduced to the irreducible minimum.

State departments of health may aid in decreasing pellagraphobia by separating the statistics of deaths from primary, now called endemic, pellagra from those reported as being secondary to many diseases. For instance the death of an alcoholic, who has pellagra when he dies, should not be reported as a death from pellagra but from alcoholism, with pellagra as a contributing factor. A not inconsiderable number of cancer victims, particularly when the esophagus, stomach, colon, and rectum are the primary seats of the disease, die from starvation and liver insufficiency, though they develop pellagra in the terminal weeks or months of their illness. Many victims of ulcerative colitis and other chronic diseases of the gastro-intestinal tract develop pellagra before they die. Such deaths should be reported as being due to cancer or other primary disease, with pellagra as a contributing cause.

It is important in getting accurate statistics to know how many deaths occur from primary pellagra and how many deaths occur from alcoholism, cancer, and chronic gastrointestinal diseases in which secondary pellagra develops and may be a contributing cause of death.

I submit the fact that the South has made wonderful progress in reducing the ravages of pellagra, malaria, hookworm, amebic dysentery, and typhoid fever in the first four decades of the twentieth century, and I insist that the people of the United States should be informed that the South is as healthy as any other section of the United States, in spite of the fact that in a few localities there exist a comparatively small number of cases of primary pellagra and malaria. The world should know that Southern health officials are aware of unfavorable conditions for health that exist in each state, and that they are doing their utmost to eradicate pellagra and malaria. The formerly dreaded yellow fever was driven from the South thirty-six years ago, never again to interfere with the health or prosperity of

the most favored section of the greatest nation on earth, and if the present rate of decrease in the incidence of pellagra and malaria is maintained, in less than a quarter of a century these and other tropical diseases will cease to exist in the region of the Western hemisphere blessed with the most favorable twelve months a year climate It, therefore, appears that the prediction of the greatest sanitarian in the history of the world, General William Crawford Gorgas, will come true, and the South will become the center of population and industry in the United States

SECTION VII

TREATMENT

CHAPTER XXIX

SPECIFIC THERAPY NICOTINIC ACID AND LIVER IN PELLAGRA

The treatment of pellagra consists of (1) specific therapy, i e, the use of nicotinic acid, liver extracts, and liver, (2) dietary management, (3) the use of drugs in the treatment of symptoms and complications, and (4) psychotherapy, not the least important procedure for the permanent cure of the patient

The Arsenic Era—During the last thirty four years, physicians who treat pellagra have witnessed the coming and passing of many so called pellagra specifics In 1906 when the disease was found to be endemic in the southern part of the United States, Lombroso's corn toxin theory was generally accepted, and his treatment with arsenic which was supposed to neutralize the effects of "pellagrozein," was considered specific Every few months physicians would report large series of patients treated successfully by various preparations of arsenic Fowler's solution of arsenic was lauded by many as a specific in the treatment of pellagra Then sodium cacodylate became the pellagra specific, and many physicians reported remarkable results with the use of pellagra "shots" One Mississippi physician recently told me that he had treated a hundred cases of pellagra with sodium cacodylate without a death

A Johns Hopkins professor in 1910 lauded elarson (arseno chlorbehenolate of strontium) as a cure for pernicious anemia I saw one of his cases of pernicious anemia cured by elarson, in which the red blood count had increased from about 1,000,000 to 4,500,000 I reasoned that if elarson would cure pernicious anemia it certainly ought to cure pellagra, and I admit that I used a barrel of the then new "French lipoid preparation of

arsenic" in treating pellagra and anemia of all varieties Since over a period of a year I had no deaths from pellagra I believed that elarson was the long dreamed of specific for the new and dreaded disease It should be added that I also used forced feeding in treating the cases of pellagra "cured by elarson"

About a year later I was disillusioned about elarson when the woman who had been "cured" of Addison's anemia at Johns Hopkins Hospital by the use of elarson came under my care because, at about the age of sixty, she had begun to "menstruate again" She had no pain and no symptoms suggesting uterine cancer, and had not had a pelvic examination until her "menses" reappeared after "missing" fifteen years A digital vaginal examination revealed an inoperable carcinoma of the uterus about the size of a small grapefruit An ambitious young surgeon removed the uterus The operation was a success but the woman died a few days later The woman, who by the way, also had achylia, had been given the "Weir Mitchell rest cure" which included forced feeding, at the Johns Hopkins Hospital, at the time her blood count increased so dramatically while taking elarson After this experience I omitted elarson in treating pellagra but continued the forced feeding and my pellagra patients continued to get well

Following Ehrlich's announcement that salvarsan, "606," now known as arsphenamine, was a specific in syphilis, when given intravenously, at twenty five dollars a "shot," that arsenical was employed by a number of physicians as a specific for pellagra They reported many cases cured when other remedies had failed The arsenical era in the treatment of pellagra lasted for ten years

The Unbalanced Diet Era—The announcement by the United States Public Health Service in 1916 that the cause of pellagra had been discovered by Goldberger to be due to an "unbalanced diet, deficient in proteins (certain amino acids)", and that the cure of the disease consisted simply in giving beans, meat, eggs, and milk to the poverty stricken victims ushered in the unbalanced diet era The advocates of the "unbalanced diet" theory insisted that no medicines were necessary in treating pellagra, that good food should reduce the mortality of the

"scourge of the South" to "two per cent" The era of drug nihilism in the treatment of pellagra was in vogue for a decade

The Yeast Era—The yeast era began about 1926 when Goldberger and his associates proved to the satisfaction of a large proportion of the medical profession that vitamin B contained a pellagra preventive substance, the "P P factor," and that since yeast was rich in vitamin B the brewers and bakers could supply the cure for pellagra Knowing the value of publicity, and needing business in the prohibition era, the makers of brewers' yeast filled the newspapers with propaganda to educate the public that while bakers' yeast would cure most diseases, "only brewers' yeast would cure and prevent pellagra" Millions of pounds of brewers' yeast were dispensed, at so much per pound, to the poor sharecroppers to prevent pellagra, and soon the druggists were treating more pellagra than the doctors Then there was an epidemic of pellagraphobia when neurotics, who try every new drug once, diagnosed their own cases as pellagra and "cured" themselves with yeast purchased over the counter at drug stores

I would not discount the really brilliant achievement of Goldberger and his associates in developing his pellagra preventive factor in vitamin B nor would I belittle the value of yeast as an adjunct to good food in curing pellagra, but in writing a factual review of pellagra specifics the fermenting yeast era should not be forgotten

The Liver and Liver Extract Era—When Minot and Murphy proved that liver and liver extracts would cure pernicious anemia, it was but natural that many physicians who regard pellagra as a nutritional disease, allied or related in some way to Addisonian anemia, began using liver and liver extracts in the treatment of pellagra They found that liver and liver extracts are as specific in treating pellagra as they are in curing macrocytic anemia I believe that liver has a permanent place in the diets for the prevention and cure of pellagra I also am convinced that liver extracts, for both oral and parenteral administration, will continue to be used in the treatment of pellagra

The Nicotinic Acid Epoch and Era—The liver era had not entirely supplanted the yeast era when Elvehjem in 1937 found

that nicotinic acid, extracted from liver would cure blacktongue in dogs and suggested its use in pellagra Then the nicotinic epoch and era began Sebrell and other laboratory investigators found that nicotinic acid will cure and prevent blacktongue in dogs, and now veterinarians and the dog owners, who have the money to buy nicotinic acid, are treating all the maladies with which canines are afflicted with nicotinic acid Dog biscuits containing nicotinic acid and other vitamins are now on the market and in general use by dog fanciers

Following the publication of the remarkable results obtained in treating human pellagra with nicotinic acid, enterprising manufacturers of this synthetic vitamin began sending literature to physicians announcing that nicotinic acid not only would cure pellagra but that it was beneficial in the treatment of "borderline deficiencies" Detail drug men, many of whom tell gullible doctors how to practice medicine, were active in calling on physicians, explaining to them how to use nicotinic acid and other vitamins Soon prescriptions for nicotinic acid and other vitamins, with trade names, filled the files of the drug stores, thus increasing the cost of medical care for their trusting patrons

The newspapers announced that nicotinic acid was the cure for the "scourge of the South" and filled their columns with pseudoscientific articles on all the vitamins Today every druggist in the nation has a display of vitamins, with trade names, manufactured by the same pharmaceutical houses whose owners have exploited the medical profession in their propaganda for profit in introducing the various vitamins with trade names Nicotinic acid is a constituent of most of the vitamin complexes sold over the counter in drug stores, and a gullible public of self diagnosticians and self prescribers now take vitamins for what the public has learned to call "borderline deficiencies"

In calling attention to the abuses of nicotinic acid therapy that have been foisted on the medical profession and an unsuspecting public, I have no intention of discounting the value of nicotinic acid as a specific in the treatment of pellagra On the contrary I am convinced that a deficiency of nicotinic acid, the pellagra preventive factor in vitamin B complex, is the

essential factor in the production of pellagra and that nicotinic acid should be used routinely in the treatment of pellagra I believe that the nicotinic acid era will endure and that the next *problem in pellagra research is to prove the nature of the underlying factors* both extrinsic and intrinsic, in the so called endemic, alcoholic and secondary types of pellagra

Nicotinic Acid Dosage —From 100 to 250 mg of nicotinic acid a day, divided into from five to ten doses, tablets of 20 mg or 50 mg, each, will clear up all the symptoms of the average uncomplicated case of pellagra in a few days Improvement in the oral gastrointestinal and neurologic manifestations of the average case of pellagra may be expected within twenty four hours, and in a few days all the symptoms, including the erythematous rash will subside If there is no improvement in two or three days the dose should be increased to 200 mg, or to 500 in each twenty four hours Where there are deep seated ulcerations in the mouth and secondary infection of the skin lesions, a longer time and often larger dose of nicotinic acid will be required for healing It should be stressed, however that while nicotinic acid will clear up the symptoms of pellagra, it is important at the same time to prescribe an adequate well balanced diet, rich in all the vitamins because the permanent cure of the patient depends upon an improvement in his general state of nutrition

The dosage of 100 to 250 mg of nicotinic acid should be continued for two or three weeks, when if the patient is getting a pellagra curative diet and he is increasing in weight and is gaining strength the dose may be diminished 50 per cent, omitting one half the tablets, every other dose When the pellagrin has gained to his normal in weight and has regained his strength sufficiently to return to his regular occupation, a prophylactic dose of 50 mg morning and evening should be continued for two or three months If the pellagrin for economic reasons cannot have a pellagra preventive diet the nicotinic acid should be continued indefinitely in prophylactic doses The average maintenance dose after recovery ranges from two to three 50 mg tablets (100 to 150 mg) a day

While from 100 to 250 mg of nicotinic acid a day is required in the average case of uncomplicated pellagra, the dose in

each individual case must be determined by the physician If the pellagrin is fairly well nourished and of the ambulatory type, treatment may be begun by giving one 50 mg tablet three times a day after meals If the patient shows improvement in twenty four hours, that dosage should be continued If there are no signs of improvement within two days, the dose may be doubled by adding a tablet three hours after meals, and two days later if there is no improvement, one 50 mg tablet should be given every two hours day and night until ten tablets (500 mg) are given in twenty-four hours Spies prefers to give small doses at two hour intervals rather than larger doses two or three times a day

Frequent and large doses are required in the acute and severe cases of pellagra to maintain the nicotinic acid content of the blood at normal, or higher than normal, levels, because in such cases it is probable that hepatic insufficiency exists in such degree that the pellagra curative factor is not stored in the liver, and it has to be replenished at short intervals Besides, in giving the smaller doses every two or three hours, there is less likelihood of reactions

Nicotinic Acid Reactions —Nicotinic acid reactions are mild, consisting of flushing, and a burning sensation or itching of the face, neck, and upper part of the body Sometimes there is itching of the whole body No serious reaction from the use of nicotinic acid has been reported Ruffin and Smith found that very uncomfortable effects followed the use of 1,000 mg daily doses of nicotinic acid when given to healthy college students The symptoms they observed were " marked mental depression, epigastric distress substernal oppression, headache, nausea and vomiting "

I have observed that the nicotinic acid reaction is less likely to occur in severe cases of pellagra than in the subclinical cases This may be accounted for by the evident fact that in acute and severe pellagra the nicotinic acid content of the blood is low and the patient does not get an overdose with the added nicotinic acid, whereas in the normal person, or those with only mild degrees of nicotinic acid deficiency, the added dose raises the nicotinic acid content of the blood to the level at which reactions

occur The analogy of the dosage of insulin for diabetics and for normal persons may be cited Ten units of insulin given to the normal person when fasting will produce hypoglycemic symptoms, because it adds enough insulin to the normal endogenous insulin content of the blood to give him an overdose, whereas 30 to 60 units of insulin given to the severe diabetic will add to his comfort and enable him to metabolize an adequate diet

Ruffin and Smith Spies Sydenstricker and others have noted that a nicotinic acid reaction is more likely to occur when the drug is given intravenously In order to prevent reactions when nicotinic acid is given intravenously, I buffer it with dextrose in normal salt solution The contents of an ampoule containing 50 mg, or 100 mg, of nicotinic acid is added to 500 to 1,000 c c of a 5 or 10 per cent solution of dextrose in normal salt solutions, with instructions to be given intravenously and slowly

Sebrell and Butler have observed reactions from nicotinic acid in doses as low as 30 mg a day in the continued treatment of pellagra It may be that as the pellagra patient improves the nicotinic acid content of his blood is raised and that the added dose will raise the nicotinic acid level to the point at which a reaction will occur, just as the diabetic convalescing from an acute infection will have reactions on the same dosage required to prevent hyperglycemia and glycosuria during his illness

No reference to the relative frequency of nicotinic acid reactions occurring when given on an empty stomach, or after eating, has been found in the multitude of articles on nicotinic acid therapy in pellagra, but it seems probable that when given before meals it will be absorbed more rapidly and the full effects obtained quickly, whereas if given after meals, there is little absorption from the stomach and as small quantities of nicotinic acid mixed with food are emptied into the intestines at one time, it is absorbed less rapidly and the nicotinic acid content of the blood and liver is maintained at a lower level If this reasoning is not fallacious it would seem that nicotinic acid reactions should occur oftener when given on an empty stomach, and that if one desires rapid results from a given dose of nico

tinic acid it should be given before meals, and when the stomach is empty It is probable that reactions would be less likely to occur if the *nicotinic acid tablets are given after meals* It, therefore, would seem advisable in the average case of uncomplicated pellagra without nausea, *to administer nicotinic acid after meals*

Spies, Sydenstricker John Youmans and others have *found* that nicotinic acid amide is effective in the treatment of pellagra without producing reactions For that reason Youmans prefers using nicotinic acid amide to nicotinic acid in the treatment of pellagra The dosage is the same, but nicotinic acid amide costs the patient two and one half times as much as nicotinic acid For that reason its use is almost prohibitive to the average pellagrin, except when treated in an endowed hospital Nicotinic acid amide is dispensed in tablets of 50 mg each and in *1 c c ampoules each containing 50 mg of nicotinic acid amide,* for parenteral use

Nicotinic Acid in the Severe Cases—*In the acute and severe* cases of pellagra, particularly when associated with painful stomatitis, vomiting, diarrhea, mental symptoms, and emaciation, nicotinic acid should be administered intravenously in 5 or 10 per cent glucose in normal salt solution Ampoules containing 50 mg and 100 mg of nicotinic acid are on sale at all drug stores If a reaction occurs from the parenteral use of nicotinic acid nicotinic acid amide should be substituted It may be added that glass containers holding 500 c c and 1,000 c c of 5 and 10 per cent glucose solutions are also *on the market* and should be used by the general practitioners and in all hospitals *except in large hospitals equipped to prepare intravenous* solutions Few hospitals, except those connected with teaching institutions, are equipped to prepare such solutions, and unless glucose solutions for intravenous use are scientifically prepared severe reactions will be frequent

The acute and severely ill pellagra patient, particularly when there is associated vomiting and diarrhea, is more or less dehydrated He therefore *needs fluids and sodium chloride* Unless there is cardiac weakness he should have 1,000 c c of 5 or 10 per cent glucose solution in saline intravenously every eight

hours or 500 c c every four hours The contents of a 50 mg ampoule of nicotinic acid may be added to the intravenous solution If the intravenous dextrose is given only every eight hours, the contents of an ampoule containing 50 mg nicotinic acid may be given intravenously and slowly with a large glass syringe four hours after the doses given in the glucose solutions If the 50 mg doses intravenously do not improve the condition of the mouth and tongue, or if they do not decrease or stop the vomiting, diarrhea, and mental symptoms within twenty four hours, 100 mg doses of nicotinic acid in salt solution, preferably dispensed in ampoules should be substituted for the 50 mg doses Sydenstricker reports one case of severe pellagra in which he used 1,000 mg a day without improvement It is interesting to note that Sydenstricker's patient with severe pellagra who failed to respond to nicotinic acid was cured by the use of liver extracts parenterally

The Nicotinic Acid "Honeymoon"—Nicotinic acid therapy may be enjoying its "honeymoon" at this time, and with more experience in treating pellagra with the new specific the "magic cures" will be less in evidence Already nicotinic acid amide is replacing nicotinic acid in the treatment of pellagra, because it is less likely to produce reactions Neither nicotinic acid, nor any other drug will cure every case of pellagra For instance, in pellagra secondary to cancer of the gastrointestinal tract, or of the liver, or to ulcerative colitis, or to other disease in which there is irreparable pathology the use of nicotinic acid may give temporary relief from the oral gastrointestinal and other symptoms of pellagra, but it will not cure the patient

There is a great deal more to treating pellagra than giving nicotinic acid It is the duty of the physician who treats pellagra to find the underlying factors which have produced the nicotinic acid deficiency, and remove them It may be that deficiency in diet, or gastrointestinal infections or infestations, or alcoholism, or some other factor which causes gastric and liver insufficiency, is the primary cause, and unless the patient can change his habits of life, or the primary disease can be cured, the use of nicotinic acid will give only temporary relief of symptoms and will not cure the patient

There has been so much newspaper publicity on the "magic cures" of pellagra by the use of nicotinic acid that the average layman believes that the cure of pellagra consists in taking a few doses of the new specific. While nicotinic acid should be used routinely in the treatment of pellagra, the physician should explain to his patient that his hope for a permanent cure lies in changing his eating habits and in so regulating his life that he can be restored to permanent health. The use of nicotinic acid in the treatment of pellagra does not lessen the importance of diet in the treatment of the disease. Indeed the dietary management of pellagra is more important than the use of nicotinic acid in the permanent cure of the disease.

The Cost of Nicotinic Acid.—The medical profession and mankind in general owe much to pharmaceutical manufacturers who maintain, at great expense, research chemical and nutritional laboratories. Drug manufacturers spent large sums of money in synthesizing nicotinic acid and in providing research workers with the drug for experimental purposes. They also devised methods of manufacturing nicotinic acid on a large scale, and it has cost large sums of money. It was to be expected that the first batches of nicotinic acid manufactured would be very expensive, but it does seem that at this time, considering the enormous quantities sold in the last two years, the cost to pellagrins, most of whom have not the money to buy food, is inordinately high.

On January 26, 1940, the date on which this chapter was written, the wholesale and retail prices of nicotinic acid tablets and ampoules in Birmingham were as follows:

WHOLESALE		COST TO PELLAGRINS	
20 mg. tablets	$ .60 per hundred	20 mg. tablets	$ .90
50 mg. tablets	$1.35 per hundred	50 mg. tablets	$2.03
100 mg. tablets	$[illegible].70 per hundred	100 mg. tablets	$4.05

Nicotinic Acid Ampoules

WHOLESALE	COST TO PELLAGRINS
100 mg. in 10 c.c. $1.80 per box of six	100 mg. in 10 c.c. $2.70 per box of six

The severely ill, poverty stricken pellagrin who takes 500 mg., ten 50 mg. tablets, of nicotinic acid a day has to spend twenty cents a day for the amount required to control his symptoms.

In addition he has to buy dilute hydrochloric acid and other drugs needed to treat various symptoms and complications, not to mention the cost of the food which is as necessary as the nicotinic acid to complete the cure of his case After the symptoms of pellagra subside, the poor pellagrin has to spend an average of ten cents a day for several months for nicotinic acid besides the necessary food to maintain health until he is completely cured

The acute and severe cases of pellagra are seen largely in undernourished individuals who have pellagra because they have not the money to buy the proper food It is in such cases that nicotinic acid has to be administered intravenously, and since 600 mg of nicotinic acid in ampoules cost the patient $2 70 a day, its use is prohibitive to most pellagrins, except in endowed charity hospitals

Preparation of Nicotinic Acid for Parenteral Use —The cost of nicotinic acid solutions for parenteral use may be reduced by about 75 per cent if the physician will buy the nicotinic acid powder and make his own solution according to the experience of one general practitioner Ruffin and Smith in the *Southern Medical Journal,* January, 1939, outline a simple method of preparing solutions of nicotinic acid in normal saline solution It is as follows

"The parenteral solution was prepared by dissolving nicotinic acid in normal saline solution so that 1 c c contained 5 mg This was sterilized by boiling or autoclaving since it has been shown that nicotinic acid is heat stable For intramuscular use the solution was injected undiluted and produced only slight discomfort There was no local reaction When used intravenously the solution was added to 500 c c of 5 per cent glucose in normal saline and administered slowly "

Ten cubic centimeters of this solution in saline will contain 50 mg of nicotinic acid which may be given intramuscularly, or intravenously, at intervals of from three to six hours in the severe cases of pellagra, until the patient can take the nicotinic acid by mouth

It is hoped that the manufacturers of nicotinic acid will be willing to reduce the price of this specific drug to a class of patients who have not the money even to buy food If not, it is suggested that the United States Public Health Service and

State Departments of Health buy nicotinic acid in large quantities and dispense it to physicians free to be administered to needy, or to all pellagrins, as is now done with arsphenamine in the cure and prevention of syphilis I would reiterate, however, that I do not believe nicotinic acid should be dispensed in large quantities to all the inhabitants of any section in the South as was done with yeast I do believe, however, that the State Departments of Health or United States Government relief agencies should provide nicotinic acid in pellagra curative and pellagra preventive quantities to known indigent pellagrins

Cheap Liver Products —It is probable that twenty cents a day spent for liver and other good food will provide enough of the pellagra protective factor to maintain the convalescent pellagrin in health or until he can be restored to health and become self supporting again Before the nicotinic acid era, I had poor patients who could not pay for liver extracts and who were living in the country and could not buy fresh liver, who have cured themselves of pellagra, sprue, and pernicious anemia by eating a ten cent can of Armour's "liver sausage spread" a day Some of them have maintained their health and have kept their blood count up to normal for several years on a ten cent can of liver a day Grocers sell a dozen cans of Armour's "liver sausage spread" for ninety cents to such patients, so that it actually costs them eight and one half cents per day to cure and protect themselves from pellagra, sprue, or pernicious anemia

Yeast —The value of yeast in the treatment of pellagra has been so exploited in newspapers and magazines that the patient who correctly, or incorrectly, has diagnosed his case as pellagra usually has been taking yeast for some time without relief of symptoms before he consults a physician It may be added that many people who have pellagraphobia, without a symptom of pellagra, have taken yeast without benefit, before they seek medical attention

I admit with some degree of pride that I have used very little yeast in the treatment of pellagra, for the reason that I believe that the 8 known component factors in vitamin B are so widely distributed in cheap and easily accessible foods, that usually it is not necessary to prescribe expensive commercial concentrated preparations of vitamins in treating the great majority

of vitamin deficiency diseases, including pellagra I also believe that the most enthusiastic of the yeast advocates have reported no better results from the use of yeast than have many physicians who by reason of experience and observation, have developed some degree of "sales resistance" to commercialized preparations that "cure diseases by magic" If yeast is a specific in the treatment of pellagra, many yeast taking pellagrins would never have consulted their physician

It has been demonstrated beyond any reasonable doubt that yeast is rich in vitamin B, including nicotinic acid, but pellagra usually is a chronic condition the cure of which depends most upon teaching the patient to eat foods with adequate vitamin content, and when the physician prescribes yeast, the patient who has read of "the magic cures of pellagra by yeast" feels that it is not so necessary to follow the diet when he can cure himself with yeast The sooner pellagrins and physicians who treat them, forget about yeast and the sooner the pellagrin and his doctor realize that yeast never cured a case of pellagra without the use, and the long continued use, of food adequate in carbohydrate, protein, and fat content and rich in all the vitamins, the better it will be for the patient who has pellagra In this connection I would again stress the fact that there is more to the treatment of pellagra than using yeast or nicotinic acid, and telling the pellagrin to eat a well balanced diet There is no disease which tests the skill of a physician more than pellagra It should be remembered that yeast is not a medicine but that its use in supplying the vitamin deficiency in pellagra is really a part of the dietary management

If the physician feels that he must prescribe yeast, the dosage usually is two level teaspoonfuls, the equivalent of 15 to 30 Gm of dried brewers' yeast, three to six times a day

The diets prescribed in the treatment of pellagra as outlined under the dietary management contain adequate amounts of nicotinic acid and thiamin In the chapter on "The Prevention of Pellagra" lists of foods rich in nicotinic acid, the pellagra preventive factor and other component factors in vitamin B complex are given

Thiamin Chloride (B_1) in Pellagra—Spies and other clinicians with large experience in treating pellagra have found that

vitamin B_1 (thiamin chloride) deficiency exists with nicotinic acid deficiency in pellagrins and that it is necessary to administer thiamin in order to complete the cure in many cases of pellagra. The fact is that most physicians who treat pellagra also use thiamin in addition to the nicotinic acid needed to clear up the pellagra symptoms. The cost of thiamin also is an item of importance to poor pellagrins in addition to the expense of using nicotinic acid.

Spies, Blankenhorn, and their associates showed that alcoholic polyneuritis is clinically and pathologically the same as the polyneuritis associated with endemic pellagra. In a more recent study, Spies, Chinn, and J. B. McLester found that the polyneuritis in 31 cases of endemic pellagra "disappeared following treatment with a well balanced diet supplemented with large amounts of vitamin B complex." Spies and Aring showed that "the pain and numbness associated with six cases of pellagra (two endemic and four alcoholic) remitted promptly following treatment with crystalline vitamin B_1. In three of the cases nicotinic acid produced rapid healing of the mucous membrane lesions." Williams and Spies advise that vitamin B_1 should be used in the treatment of polyneuritis of endemic and alcoholic pellagra.

A favorite method of administering thiamin chloride (B_1) is in ampoules containing 3,000 international units of vitamin B_1. The contents of one or two ampoules are administered parenterally a day. The wholesale cost of a box of six thiamin chloride ampoules is $1.35, and the "fair price," retail, cost to the poverty stricken pellagrin is $2.03, from thirty five to seventy cents a day for an adjunct to nicotinic acid in the treatment of a poor undernourished pellagrin who has not the money to buy sufficient food to keep him in health.

When thiamin chloride is administered orally it usually is combined with nicotinic acid, the pellagra preventive factor, formerly called B or vitamin G. Each capsule contains "333 international units of B_1 (1 mg. of thiamin chloride) and 40 Sherman units of vitamin B (G), with other factors of vitamin B complex from liver stomach concentrate." In order to give an adequate dose, at least two capsules of vitamin B complex

must be given three times a day. The cost, "fair price," to poor pellagrins is as follows:

WHOLESALE PRICE		"FAIR PRICE" (RETAIL)		
40 capsules	$1.20	40 capsules	$1.80	(4½ cents each)
500 capsules	$11.88	500 capsules	$17.82	(3½ cents each)

Few pellagrins can buy 500 B complex capsules at a time. Therefore, if six of these B complex capsules are given a day, it costs the poverty stricken victim of pellagra twenty-seven cents a day, besides the dilute hydrochloric acid and other drugs which may be needed to treat symptoms and complications in addition to adequate food.

I would remind the manufacturers who make exorbitant profits selling nicotinic acid, thiamin chloride, and other vitamins, of the Latin proverb "verbum sat sapienti."

Riboflavin Therapy.—Ariboflavinosis, described by Sebrell, may be a serious complication of pellagra. It also may occur as a separate disease entity. Fissures in the corners of the mouth and a dirty pigmented eruption over the alae of the nose suggest riboflavin deficiency. When that occurs in the course of pellagra, riboflavin may be administered by mouth, if the patient is not very ill, but if evidences of ariboflavinosis occur in a severe case of pellagra, riboflavin should be administered with nicotinic acid, intravenously.

Riboflavin for oral administration is dispensed in capsules, each containing 1 mg. One or two capsules after meals three times a day will be necessary to clear up the symptoms in the mild cases of ariboflavinosis, either associated with pellagra, or when it occurs as a separate disease entity. The cost of riboflavin to the average pellagrin is prohibitive, except in an endowed hospital. Twenty-five capsules of riboflavin cost the druggist $2.50. If 6 mg. a day are given it will cost the poor pellagrin $1.08 a day, which when added to the cost of nicotinic acid and thiamin chloride makes its use out of the question in treating the average case of pellagra, complicated with ariboflavinosis.

Ariboflavinosis in a severe case of pellagra is a serious complication, requiring the intravenous administration of riboflavin. Riboflavin for intravenous use is dispensed in 2 c.c. ampoules,

each containing 10 mg of riboflavin Each ampoule costs the patient 50 cents, making its use prohibitive to the average person who has pellagra It is probable that the cost of riboflavin will be reduced, as ariboflavinosis is recognized more frequently and as there is increased demand for the drug

Liver and Liver Extracts in Pellagra—The addition of liver to the diet of pellagrins used since Minot and Murphy's epoch making discovery that pernicious anemia may be cured by eating liver, is one of the most important advances that have been made in the therapy of pellagra The use of liver and liver extracts in pellagra is specific therapy since they provide nicotinic acid plus many other factors which prevent pernicious anemia and allied nutritional diseases

Boggs and Padget reported a large series of cases in which the liver diet was used in the treatment of pellagra The following excerpt from their report shows remarkable results from the use of liver in the treatment of pellagra They said "In 1928 a liver diet was first employed, and since that time has been used regularly There has been no other change in the method of treatment Not only has the percentage of recoveries been greatly increased, but the average stay in the hospital has been reduced We have used liver extract in only a few cases, but have found it fully as effective as liver itself"

Ruffin and Smith credit Voegtlin as having used liver in the treatment of pellagra in 1914, and Ramsdell cites Goldberger and Sebrell as having used liver extracts in human pellagra They regarded the curative effect of liver extracts in pellagra as due to the pellagra preventive factor then called vitamin G, which it contains We now know that liver contains nicotinic acid the pellagra preventive factor

Ramsdell, in Dallas, Texas, began using liver extract parenterally in the treatment of pellagra in 1932 He used 2 c c of liver extract (No 343, Lilly) intramuscularly once a day in 25 cases without a death The patients were kept in bed on a general diet with no medication except the liver parenterally

Ruffin and Smith treated 40 cases of pellagra, in Duke University Hospital in Durham, North Carolina, with the use of liver extract, given orally and parenterally They found that

an aqueous extract of liver (Valentine's) given by mouth not only cured pellagra but prevented its recurrence in patients who after treatment were exposed to sunlight They found that the use of liver extract parenterally was effective only partially in curing pellagra Ruffin and Smith conclude that the liver extract used parenterally does not contain all the pellagra preventive substances as does the aqueous liver extract of whole liver (Valentine's) used orally

Mallory in an article on "The Relations of Pellagra to Pernicious Anemia" published in 1929, reported two cases of macrocytic anemia in pellagrins who were cured of both by the use of liver

Fresh Whole Liver —Whole liver is the best source of all the vitamins According to Sydenstricker edible whole liver contains as much as 25 mg of nicotinic acid per 100 Gm so that in feeding pellagrins liver they are getting nicotinic acid therapy in addition to other vitamins, including thiamin riboflavin, and vitamin E, which not only controls reproduction but is indispensable for general nutrition Whole liver also contains the hematopoietic factor which will prevent or control the anemia so often seen in pellagra

Most of my patients with pellagra pernicious anemia and sprue like liver, and they eat it two or three times a day until they are cured clinically They are then impressed with the importance of eating liver twice a week for the rest of their lives Many patients who do not like liver cultivate the taste for it, but occasionally a pellagrin refuses to eat liver, and it becomes necessary to use liver extracts parenterally

The remarkable cure of what was thought to be a hopeless case of pernicious anemia by the use of calf beef, or hog liver in a patient who first had pellagra in 1916 then the sprue syndrome, and finally developed pernicious anemia in about 1920, was convincing that in liver we have a potent agent in the therapy of all three diseases This case was reported in 1927 Since then liver has been added to the diets of all cases of pellagra and sprue treated in the Seale Harris Clinic The patient referred to was a well nourished wealthy planter who was cured of pellagra in 1916 on a well balanced low carbohydrate, high protein, rich vitamin diet A few years later he had sprue with

pronounced anemia, and later developed typical *pernicious anemia* He was able to buy liver, which he liked and used every day, and kept in perfect health until he was killed in a storm in 1934

Sprue and Macrocytic Anemia Cured With Liver and Liver Extracts—Another dramatic cure of a case of tropical sprue with macrocytic anemia by the use of liver may be mentioned This case of sprue presented the symptoms of a moderately severe case of pellagra, without skin lesions, and the *treatment was the same that has given similar results in severe* cases of pellagra For that reason the case will be reported in detail

A lovely woman aged 30, wife of an Army officer who had been stationed in the Philippines, developed sore tongue, nausea vomiting mushy diarrhea pronounced anemia marked weakness loss of flesh, nervousness and mental depression She had been treated for amebic dysentery several times without improvement She had grown worse in the last few weeks and her condition was considered serious when she was admitted to the Highland Avenue Baptist Hospital on May 4, 1938 Her height was five feet and she weighed 75 pounds at that time She complained of a very sore mouth, nausea, vomiting severe diarrhea, prostration and mental depression She appeared anemic and her skin had the lemon yellow tinge of pernicious anemia Her hemoglobin was 45 per cent, red blood count was 2 000 000 white blood count 7 000, and smears for malaria were negative Examination of gastric contents showed achylia Repeated examination of warm specimens of feces were negative for *Endamoeba histolytica* Her stools were large, foamy and mushy containing much fat

' She was given a blood transfusion, and 1 000 c c of 10 per cent dextrose in saline intravenously every 8 hours and no food was given by mouth for 24 hours, she also was given $3\frac{1}{3}$ c c of liver extract in the gluteal muscles daily for 3 days, then twice a week When she was able to retain food she was given one teaspoonful (4 c c) of dilute hydrochloric acid in milk with meals and 3 hours after meals Her food was increased until she was taking about 4,000 calories of a moderately low carbohydrate high protein diet, with a banana and milk 3 hours after meals and orange juice every 2 or 3 hours if awake at night She liked liver and was given fresh cooked liver for her noon meal (dinner) and canned liver for supper, and the liver extract parenterally was discontinued She returned for a check up in February, 1939 She reported that she had gained 29 pounds and had been in excellent health, her cheeks were rosy and she presented the picture of a normal, attractive vigorous woman Her hemoglobin was 75 per cent and her red blood count was 4,000 000 Examination of her stomach contents showed achylia The dilute hydrochloric acid in a glass of milk with

meals was continued She had grown tired of liver and liver extract parenterally twice a week was continued

A report received from her on February 5, 1940, said that she had continued in excellent health, but since she had gained in weight (43 pounds, total weight 118 pounds), she was beginning to fear obesity

Canned Liver—The suggestion was made to an indigent sprue patient, who had a red glazed tongue, mushy diarrhea, and whose blood count was about 2,000,000, that he try cheap canned liver He found that he could get Armour's "liver sausage spread" in ten cent cans at 90 cents per dozen, and he ate a can a day for a number of years He made a remarkable recovery His blood count went up to 4 500,000 and he increased in weight from 107¼ pounds to 162 pounds He later left off the canned liver and his blood count dropped to 1,000,000 A number of anemic patients with pellagra or sprue, who were not able to buy liver extracts, have used this cheap canned liver with excellent results It is admitted that the results from using canned liver have not been studied in a large series of cases of pellagra, but the clinical results in a number of cases have been so favorable that canned liver is advised as the one most important article of diet for the pellagrin where fresh liver is not available

Recent articles on pellagra by many authors all over the world where pellagra has been found show that liver, or liver extracts, has been used extensively, and that its use is displacing yeast therapy rapidly

There can be no doubt but that many clinicians have been using liver in some form in the treatment of pellagra since Minot and Murphy's discovery, in 1924, that the free use of liver will cure pernicious anemia The same liver diet used in pernicious anemia will also cure pellagra and sprue

I believe that whole fresh liver, or canned liver, is the best source of the pellagra preventive factor because it is rich in nicotinic acid and all the other vitamins needed to prevent and cure pellagra Another reason why whole liver is preferred in pellagra is that it is one of the best available sources of protein

Aqueous Extracts of Whole Liver—Ruffin and Smith demonstrated that the aqueous extract of whole liver (Valentine's)

will cure pellagra in cases in which the extracts used parenterally have failed It must be given in adequate doses, 90 c c (6 tablespoonfuls) a day for from a week to ten days in attacks, and after the symptoms subside, 15 c c (1 tablespoonful) after each meal (three times a day) should be continued for several weeks Occasionally patients object to the taste of liver extract and prefer to take it in tomato juice, orange juice, or milk

Liver Extracts Parenterally—The parenteral use of concentrated liver extracts is indicated when patients will not eat liver, or refuse to take the aqueous extract of whole liver by mouth, or when there is nausea Liver extract when given parenterally should be injected deep into the gluteal muscles If the injections are painful, 1 or 2 c c of 1 per cent solution of novocaine may be added to the liver extract, or may be injected into the muscles with a small needle before the liver extract is given

There are a number of liver concentrates manufactured by reliable pharmaceutical houses, but I have used Lilly's concentrated liver extract in 10 c c ampoules more than any other similar preparation When used for macrocytic anemia the dosage is 3⅓ c c, one third of an ampoule, daily for three days, then twice a week, but when given during an attack of pellagra in which liver insufficiency seems pronounced, the contents of a 10 c c ampoule should be given once or twice daily, until there is improvement in symptoms In the severe cases of *pellagra when death from acute liver insufficiency seems imminent*, the use of large doses of liver extract may save the patient's life When liver extract is used, full doses of nicotinic acid are not necessary, and the dosage may be reduced by one half If nicotinic acid reactions occur the drug may be left off altogether when liver extracts are given In the severe cases of pellagra, in addition to large doses of liver extract, nicotinic acid in 100 mg doses should be given intravenously in normal salt solution three times a day

The advantage of whole liver, the aqueous extract of whole liver, and to a lesser extent concentrated liver extract for parenteral use over nicotinic acid is that they provide all the vitamins, and no doubt other unrecognized substances, which are

needed to combat the liver insufficiency and the multiple avitaminoses which are present in the great majority of cases of pellagra While nicotinic acid deficiency is the essential cause of the symptoms of pellagra, the pellagrin usually is a sick man in other respects Osler's often repeated advice to his students, to treat the whole patient in addition to the use of special therapy for his disease certainly applies in the management of pellagra, and liver and liver extracts seem to provide the food and medication necessary to cure the protean manifestations of endemic, alcoholic, and secondary pellagra

CHAPTER XXX

DIETARY MANAGEMENT OF PELLAGRA

Treat the Patient—Lombroso's epigram "There is no disease only the diseased" provides the key for the cure of pellagra Treat the patient by building up his bodily resistance to overcome the disease In a large proportion of the mild cases, rest and an adequate diet will be sufficient, without the use of *nicotinic acid, to relieve the symptoms in an attack*, but the physician's duty in treating pellagra does not end with his *patient's convalescence* He still is a pellagrin and should be considered as such until two or three years have elapsed without a recurrence of symptoms

Since a high carbohydrate, low protein, vitamin deficient diet is recognized as an important predisposing cause of pellagra, a low carbohydrate, high protein diet, rich in vitamins A, B complex, C and E, consisting of milk, eggs, meats, liver in particular, and a variety of vegetables and fruits, seems indicated in its treatment This change in diet, if lived up to for several weeks or months, is sufficient to cure the great majority of cases of pellagra

Fluid Feeding—In beginning the treatment of pellagra, particularly when the diarrhea is severe, it may be best to limit the diet to strained fruit juices and infusions of green vegetables, which leave no residue and do not ferment readily They also supply needed fluids

"Potlicker"—Rural physicians in the South have been curing diarrheas and dysentery with "potlicker" and tender turnip greens for many years It is a sterile food rich in vitamins A, B, and C, and practical experience has proved it to be efficacious in chronic diarrhea among the poor in rural districts who have been living on a high carbohydrate, deficient vitamin diet "Potlicker" also has been found of value in treating the diarrhea of pellagra

Milk—Milk is one of the most important articles of food in the treatment of pellagra Unless certain of the purity of the

milk, it should be boiled, or pasteurized In beginning treatment, milk may be given every two or three hours, three or four ounces (90 to 120 c c) at each feeding, increasing it as the diarrhea subsides, to six or eight ounces (180 to 240 c c) and as the patient convalesces, to a pint (500 c c) five times a day

Green Vegetables—Pureed vegetables, i e , turnip greens, spinach, string beans, and other green vegetables, may be added for dinner and supper Soft cooked eggs, scraped beef, minced chicken, and tender liver and other tender meats which leave no residue may be given from the beginning of treatment

Bread—Whole wheat bread, whole grain corn meal bread, and whole grain cereals thoroughly cooked may be added to the diet unless there is nausea Cane sugar products, including syrup and desserts of all kinds are forbidden in pellagra, not only during the treatment, but for months after all symptoms have subsided

The Banana Cure—The "banana cure" for sprue has been in vogue in the tropics for many years No other food except bananas one every two or three hours day and night if the patient is awake, is given for two or three days, even when the diarrhea of sprue is pronounced

Deeks advocated the use of bananas in the diarrhea of pellagra as far back as in 1910 It is important for the bananas to be thoroughly ripe, after the starch has been changed into fruit sugar for use in the treatment of diarrhea Bananas not only provide a readily utilizable form of carbohydrate but they are rich in vitamins A, B and C

I have used bananas in my diets for the diarrhea of pellagra for many years, not as the only food but three or four ripe bananas in addition to fruit juices and milk, are given during the twenty four hours The opinion prevails among laymen that bananas are difficult to digest, and it sometimes is necessary to explain to pellagrins that a hard banana when the skin is light yellow in color may be indigestible, but that ripe bananas are so easily digested that they are given to infants when only a few months old

Diet in the Diarrhea of Pellagra—The following diet has been used successfully for many years in the treatment of the diarrhea of pellagra, and other diarrheas

Diarrhea Diet in Pellagra

2 to 4 ounces of strained orange juice, canned apple juice, or other strained, unsweetened, fruit juices every 4 hours during the day, and at night if awake

Hot "potlicker" or strained tomato juice (hot or cold) may be substituted for fruit juice

3 to 6 ounces of pasteurized or boiled milk every 4 hours day and night if awake, alternating with fruit juices giving fruit juice or milk every 2 hours

A small ripe banana may be given with the milk every 4 hours

Very tender, or pureed, turnip leaves (greens) may be given for dinner and supper Hot strained purees of spinach string beans, or green peas or other beans may be given for dinner and supper

The soft part of corn bread or muffin bread made from whole grain corn meal, or a slice of whole wheat bread dry toast cut into small squares croutons may be added to the strained vegetable soup at meals A slice of whole wheat bread may be given as hot milk toast once or twice a day The whole grain cereals, oatmeal in particular, and milk or cream without sugar, may be given for breakfast or supper Sliced bananas or scraped apples may be added to the oatmeal and milk

Two soft cooked eggs for breakfast, tender meats preferably calf liver for dinner and cottage or American cheese for supper may be added in two or three days even if the diarrhea has not subsided

Note —White corn bread, white bread of any kind, grits, and *other devitaminized foods are forbidden* Cane sugar products, including ice cream, cake, pies and other sweet desserts, and syrups of all kinds, are not allowed Coffee, tea, and the caffeine soft drinks are prohibited The pellagrin who forgets the sweet taste will get well quicker and will be less likely to have relapses

Forced Feeding —After a few days, as the patient improves forced feeding should be resorted to even if there is diarrhea, because improvement in nutrition is most important in restoring and maintaining the health of the pellagra victim

When the acute symptoms have subsided in pellagra, it is best to prepare an individual diet list for each patient, varying it to meet indications, and modifying it to suit the available food supply and the nutritional needs of the patient *It is not enough to give a diet list to a pellagrin, the physician should instruct other members of his family to see that he eats the prescribed food Pellagrins should be made to eat even if they have no appetite*

After the first few days of preliminary dieting, as outlined above, a full diet is given, approximating 4,000 calories a day, selected from the articles on the list given below. Not more than one kind of fruit, cereal, or meat is allowed at a meal, though two or three different kinds of vegetables may be given for dinner and supper. The following diet list, with general instructions, may be given to pellagrous patients who are able financially to afford a variety of food. It may be modified for the pellagrin who lives in the country and who has to choose his daily food from only a few articles of diet. This diet is practically the same diet that I have used in treating pellagra for thirty-four years.

Forced Feeding Pellagra Diet List

Breakfast

One Fruit: ½ grapefruit, orange or orange juice, ½ cantaloupe, baked apple, berries, peaches, or any other fruit in season.

One Cereal: Thoroughly cooked oatmeal or other cereals and sliced bananas or sliced peaches with milk or cream, no sugar.

Eggs and Bacon: 2 eggs cooked any way except fried, 2 or 3 slices broiled bacon.

Bread: 1 slice whole wheat bread toast, one small graham flour biscuit, or 1 corn meal muffin, or 1 small piece of corn bread made from freshly ground whole corn meal.

Butter: 2 or 3 teaspoonfuls.

Milk: 1 pint.

Three Hours After Breakfast

One pint of milk and a ripe banana, or peanut butter and crackers.

Dinner

Soup: Vegetable soup or potlicker.

Green Vegetables: (1 or 2 varieties.) Large serving of spinach, turnip greens, mustard greens, tender string beans, cabbage, squash, eggplant, okra, corn, carrots, cauliflower, Brussels sprouts, onions, etc., cooked without much grease. Lemon juice may be used freely on vegetables after they have been cooked.

Meat: Fresh liver or canned liver, tender beef steak, roast beef, lamb, chicken, bacon, thinly sliced boiled ham, fish, or oysters, cooked without much grease.

Potatoes: Baked sweet potatoes and butter.

Bread: 1 slice whole wheat bread or dry toast or small piece of country ground corn meal bread, or 1 small corn muffin, 2 pats butter.

Milk 1 pint

Dessert Peaches, baked apple, banana, or other fruit or berries with milk or cream, *no sugar*, cantaloupe or honeydew melon, or small piece watermelon, or other fruit desserts

Three Hours After Dinner

One pint of milk and a ripe banana, or peanut butter and crackers

Supper

Liver Fresh liver or canned liver or liver sausage spread

Protein Vegetables, i e baked beans, butter beans, lima beans, field peas, or English peas

Cheese Cottage cheese American or Swiss cheese

One Uncooked Vegetable Large serving of lettuce, cole slaw, tomato, grapefruit Waldorf salad Mayonnaise or French dressing

Bread One slice whole wheat bread or dry toast, or whole corn bread

Butter 2 pats

Milk 1 pint

Dessert Orange cantaloupe, baked apple, or banana and cream without sugar Fresh pineapple or other fresh fruit desserts without sugar

General Directions—Meats should not be cooked too long They are best broiled baked, or boiled Breads, cereals, potatoes, and other starchy foods should be thoroughly cooked, and should be eaten sparingly Milk is the one most nearly perfect food, and the underweight convalescent pellagrin should drink five pints (2½ liters) a day until his weight becomes normal, *then two or three glasses a day* Vegetables are essential and two or more varieties may be eaten for dinner and for luncheon or supper Raw vegetables and raw fruits are essential foods at least 1 raw fruit and 1 raw vegetable a day should be eaten

Foods to Be Avoided—*Fried foods, syrup, pies, candies and other sweets except those mentioned above No coffee, tea, coca cola* or other caffeine beverages No sweet soft drinks

Mastication—Eat slowly, a good rule is to masticate each morsel of food until no solid particles can be felt when the tongue is pressed against the roof of the mouth

Drinking Water—*Drink two glasses of cool* water, after brushing teeth on arising at least ½ hour before breakfast Do not drink more than one glassful of water with meals, and one glassful ½ to 1 hour before dinner and supper In hot weather drink *a glassful of* water every 1 or 2 hours during the day

The Taboo of Toxins—The absolute taboo of tobacco in all forms snuff cigarettes, cigars, pipes, or chewing tobacco is important The use of tobacco in any form decreases the appetite and disturbs nutrition *Nicotine* is a *toxin*, particularly harmful to undernourished individuals, and it destroys initiative in pellagrins If the money which the average

pellagrin spends for snuff chewing and smoking tobacco had been used in buying food he probably would not have pellagra

The use of all forms of alcoholic beverages by pellagrins should be interdicted for the rest of their lives whether they have the so called endemic or alcoholic pellagra Contrary to brewery propaganda there is not a vitamin in a keg of beer If all the money spent for beer, whiskey, and other toxic, narcotic habit forming alcoholic beverages by the indigent classes who are prone to pellagra was spent for food, there would be but little pellagra in the United States If the pellagrin desires to bring on a recurrence of his symptoms, he should drink alcoholic beverages

When pellagra patients cannot have hospital treatment, they should be questioned regarding the food that they can get at home, and a diet list is prepared from the food that is available It is necessary to be exact in prescribing food for pellagrins, and unless specific instructions are given, they will make but little effort to carry out a diet

Dietary Management in Convalescence—Even the poorest families in the rural districts can keep a cow, or can get milk from their neighbors They can have chickens and eggs and can raise enough vegetables for their use Green vegetables in season are important but dried peas and beans can be kept through the winter, and canned turnip greens canned tomatoes, canned tomato juice, canned beans, and other canned vegetables are cheap and contain nicotinic acid, the pellagra preventive factor Home raised meat is best, but cold storage ham, bacon, sausage, and fresh beef (steak or roast), when obtainable, should be given once a day Canned liver and other canned meats, and canned fish contain needed proteins, nicotinic acid, and other needed vitamins

McCollum's dictum of the daily nutritional needs of any adult should be followed by the pellagrin for the rest of his life, i e, 1 raw fruit, 1 raw vegetable, 2 cooked green vegetables, and 1 pint or 1 quart of milk a day, to which may be added a sufficient amount of bread, butter, and meat to make up the required amounts of carbohydrates, proteins, and fats to maintain normal weight and strength

Pellagrins and their relatives should be taught how to prepare food Many of the diseases among the poor in which malnutrition is a contributing factor can be traced as much to improper cooking, and imperfect mastication, as to the poor quality and

insufficient quantity of the food ingested The poor in the country do not cook their bread and cereals thoroughly but cook their meats too long

When every family in the rural districts has a cow, chickens, eggs, a bountiful garden, and a few fruit trees and when they learn how to prepare their food properly, pellagra, tuberculosis, insanity, and other chronic conditions in which malnutrition is an important predisposing factor, will be among the rare diseases

Food Every Three Hours—One of the most important recent contributions to the *study of nutrition was published by* Howard W Haggard and Greenberg (*Diet and Human Efficiency,* Yale University Press, 1938) in which they showed that the average normal individual may add approximately 10 per cent to his efficiency by taking food three hours after breakfast and the noon meal An added reason for the pellagrin to eat between meals is that the liver does not store appreciable quantities of vitamin B, including the pellagra preventive factor, and the utilizable nicotinic acid content of the liver must be replenished constantly by taking food often

Pellagrins are prone to suffer from insomnia, and the best remedy for sleeplessness is a glass of milk, or a banana, or orange juice at bedtime and every two or three hours if awake at night

For the above reasons in prescribing diets for pellagra, it is important to insist that the patient take food three hours after meals, at bedtime, and every two or three hours if awake at night

Diet for the Cured Pellagrin—After all the symptoms of pellagra have subsided and the pellagrin has gained in weight and strength to normal, he should continue to live on a pellagra preventive diet Such a diet should contain not only the proper amounts of carbohydrates, proteins, fats, and minerals, but should be rich in all the vitamins, including the pellagra preventive factor in vitamin B

The following diet, an optimal dietary regimen for the average adult, if adhered to will prevent recurrence of pellagra in the average cases of endemic pellagra

Pellagra Preventive Diet

Breakfast

One fruit ½ grapefruit orange or orange juice, ½ cantaloupe, baked apples berries peaches or any other fruit in season

One Cereal Small portion of thoroughly cooked oatmeal, or other cereal with milk or cream No sugar

2 Eggs and 2 or 3 slices breakfast bacon

Bread 1 slice whole wheat bread toast or 1 small graham flour biscuit

Butter 2 or 3 pats (teaspoonfuls)

Milk 1 glass whole milk

Three Hours After Breakfast

Milk or fruits in season or bread and butter or crackers and peanut butter

Dinner

Soup Chicken beef or vegetable soup potlicker, or tomato juice

Green Vegetables (1 or 2 varieties) Large serving of spinach turnip greens mustard greens tender string beans cabbage squash eggplant okra corn carrots cauliflower Brussels sprouts onions etc cooked without much grease Lemon juice may be used freely on vegetables after they have been cooked

Meat Liver chicken turkey mutton roast beef tender steak bacon thinly sliced boiled ham or fish cooked without much grease

Bread 1 slice whole wheat bread or dry toast or small piece of country ground corn meal bread or 1 corn muffin

Milk Glass of whole milk or buttermilk

Dessert Peaches baked apple banana or other fruit or berries with milk or cream no sugar cantaloupe or honeydew melon or small piece watermelon or other fruit desserts

Three Hours After Dinner

Milk, or fruits in season or bread and butter or crackers and peanut butter

Supper

One Meat Substitute Protein vegetables i e, baked beans butter beans lima beans field peas or English peas, or cottage cheese American or Swiss cheese

One Uncooked Vegetable Large serving of lettuce, cole slaw tomato grapefruit, Waldorf salad Mayonnaise or French dressing Celery radishes

Bread 1 slice whole wheat bread or dry toast 1 pat butter

Milk One glass of whole milk, or buttermilk

Dessert Orange, cantaloupe baked apple or banana and cream, without sugar Fresh pineapple or other fresh fruit desserts without sugar

Bedtime and Night Feedings

A glass of milk, or banana, or orange juice at bedtime and every two or three hours if awake during the night

Dieting the Rural Pellagrin —It is recognized that the indigent pellagrin in the rural districts cannot get all the articles of food listed on the above pellagra preventive diet In such cases the physician should discuss with the family the available foods and prescribe a diet which the pellagrin can get

Since the average pellagrin in the rural districts was living on a diet consisting largely of corn bread, made from Western ground devitaminized corn meal, white grits, fried side meat, and syrup, when he developed pellagra, it would seem advisable for him to substitute wholesome food of better nutritive value The physician therefore should instruct the pellagrin, and his family, as to why it is necessary to stop using the foods deficient in vitamins The pellagrin should be told that under no circumstances should he eat corn bread made from Western ground corn meal, but that he should substitute country ground meal, or other freshly ground, whole grain corn meal, for the "dead" corn meal he has been eating Whole wheat flour bread may be substituted for corn bread

Endemic pellagra did not exist in the South when the inhabitants of the rural districts ate fresh, rock ground corn meal Recently I had the privilege of visiting a garden in Aberdeen, Mississippi, in which the owner of the home had constructed walks made of 120 mill stones Since only two stones were used to the mill, there must have been at one time 60 gristmills in the vicinity of Aberdeen, Mississippi, where farmers could have their corn and wheat ground as needed When the water mills for grinding corn and wheat in the South were abandoned, and Western ground, devitaminized, white corn meal became the principal article of food among the poor, pellagra began to take its toll among the inhabitants of the rural districts This fact is reiterated, and the slogan in the prevention and cure of endemic pellagra should be *Stop using Western ground white meal and establish small electrically driven gristmills in every rural community where farmers may carry their corn and have*

it freshly ground as needed The hand mills (family size) for grinding wheat and corn are still better, because then one is sure of getting all the vitamins contained in corn and wheat

The physician also should inform the pellagra patient and his family that they should eat less corn bread, and syrup, that a high carbohydrate diet prevents the full utilization of vitamin B, including its nicotinic acid content It is best to eliminate syrup and cane sugar from the diet of pellagrins and potential pellagrins

What foods can the indigent pellagrin in the country get? He can get eggs, milk, lean meats, and bread made from country ground corn meal or whole wheat flour He can get fruits, berries, and vegetables in season, and dried beans and peas, and cheap canned vegetables and fruits during the winter

Pellagra Curative and Pellagra Preventive Diets for Use in Rural Districts —The following is a pellagra curative and pellagra preventive diet, which may be had in the rural districts

Breakfast

Fruits in season if they can be obtained

Bread 1 or 2 pieces of bread made from freshly ground whole corn meal or 1 or 2 small biscuits made from freshly ground whole wheat

Eggs 2 eggs cooked in any way except fried, and 2 or 3 slices bacon or ham, or country sausage

Freshly ground whole corn grits or hominy or oatmeal and butter or milk

Milk 1 or 2 glasses of whole milk

Butter 2 or 3 teaspoonfuls

Honey If available

Three Hours After Breakfast

A glass of milk and or peanut butter and crackers

Dinner

"Potlicker," or any kind of soup

Meat Lean meat, ham or bacon chicken, beef or fish If home raised meat is not available cheap canned *liver*, or other canned meats may be substituted

Green Vegetables Turnip, collard, or mustard greens cabbage, string beans squash, turnips or any other garden vegetable If fresh vegetables are not available canned vegetables of all kinds may be substituted

Bread 1 or 2 pieces of whole grain corn bread, or whole wheat bread and butter

Milk 1 or 2 glasses of whole milk

Fruits in season peaches, apples, pears berries of all kinds, with or without milk, or watermelon, may be given for dessert

Three Hours After Dinner

A glass of milk, and, or peanut butter and crackers

Supper

"Potlicker," soups and vegetables as for dinner

Vegetables Fresh peas or beans of any variety, or dried peas or beans, or canned peas or beans will supply needed proteins, or homemade cottage cheese, or American cheese, uncooked, are good cheap meat substitutes

Uncooked Vegetables Lettuce, tomatoes, cole slaw, or other fresh uncooked vegetable if available If not, a can of tomatoes including the tomato juice, will supply needed vitamins

Bread and butter, as for breakfast and dinner

Bedtime and Night Feedings

A glass of milk or piece of whole corn bread, or whole wheat bread and butter at bedtime and every three hours if awake during the night

Foods Are the Best Source of Vitamin B—About twenty years ago McCollum expressed the opinion that in the United States, due to the almost universal use of roller mill produced (white) flour and (white) meal, and other devitaminized foods, all of which are deficient in vitamin B_1, there are many border line cases of polyneuritis It seems probable that in pellagra vitamin B_1 deficiency, short of producing polyneuritis, must be common, and that many of the vague nervous symptoms common in pellagra may be due, in part at least, to a deficiency of vitamin B_1 It, therefore, would seem advisable in the treatment of all cases of pellagra to use diets rich in all the component factors of vitamin B The fact is they are found together in many common foods Indeed, there are few articles of diet rich in vitamin B_1 that are poor in the pellagra protective factor

The diets which I have been using, not only in the treatment of pellagra but in all other diseases, including peptic ulcer ("The Role of Vitamins in Peptic Ulcer," J A M A) and

diabetes mellitus ("The Etiology and Prevention of Diabetes," Virginia M Monthly 50 672 1924), have called for breads made from whole wheat flour, and country ground corn meal, and liberal quantities of fruits and vegetables Since Alfred McCann began his crusade against the use of "white flour, white corn meal, white rice, white sugar and other "devitalized" foods, as McCann called them forty years ago, before the discovery of vitamins, I have used whole wheat and whole corn products in my home and I also eliminated white bread from prescribed diets at least thirty years ago

The diets listed in this chapter differ but little from the 'forced feeding' diets which I used in treating my first cases of pellagra in 1907 I advocated 'forced feeding' in discussing the treatment of pellagra at the Gulfport Pellagra Conference in 1909 (Gulf States J Med January 1910) and in an address before the Texas State Medical Association in 1914, published in the *Texas State Medical Journal* It should be added that these diets differ but little from those advised for pellagra by H F Harris and many others since they began treating the disease These 'forced feeding" diets are essentially the same as those advocated by Weir Mitchell fifty years ago as a part of the regimen in his 'rest cure

Reference to these diets shows that they contain not only adequate amounts of carbohydrates, proteins, and fats, but they contain sufficient quantities of vitamins as measured by recent estimates of the vitamin content of various foods Williams and Spies estimate that a 1 000 calorie well balanced diet should contain about 275 international thiamin units My pellagra diets containing 3,500 to 4 000 calories a day, are high in proteins, with a total thiamin content of at least 1,000 international units

Vitamin A—Underhill and Mendel produced blacktongue, or a condition closely resembling it, in dogs by feeding them diets deficient in vitamin A The Committee on Vitamins of the American Public Health Association was so impressed with the work of the Yale investigators that it advised further studies of vitamin A deficiency in pellagra

Mellanby, by feeding animals diets deficient in vitamin A, carotene, produced the cord lesions common to pellagra and

pernicious anemia By feeding dogs on a pellagra producing diet, with adequate amounts of carotene, he prevented the cord lesions It seems possible that a deficiency of vitamin A may be a factor in producing the cord complications seen in neglected cases of pellagra

McCollum and others have pointed out that general nutrition suffers on diets deficient in vitamin A It, therefore, seems important in treating pellagrins to prescribe adequate quantities of vitamin A It is unnecessary *to prescribe expensive proprietary* preparations of vitamin A, because adequate quantities may be given in liver, milk eggs, and the green and yellow vegetables Certainly the so called pellagra producing diets upon which the poverty stricken people of the South are supposed to subsist are deficient in vitamin A Therefore, in preparing diets for pellagrins, foods rich in vitamin A should be included The diets usually advised in pellagra are rich in vitamin A, and it is probable that the improvement in the general nutrition following the use of foods of high vitamin A content is a factor in curing many cases of pellagra

Vitamin C—J N Roussel, of New Orleans, regards pellagra as a manifestation of scurvy and has used lemon juice in its treatment since 1910 In 1918, in a paper read before the Louisiana State Medical Association, he reported a large series of cases cured of pellagra by the use of 3 or 4 lemons a day for two or three weeks He regards the fact that lemon juice, rich in the antiscorbutic vitamin (ascorbic acid) without medication, cures pellagra as proof that the disease is due to a deficiency *of vitamin C* A L Levine, Professor of Gastro Enterology in the Medical Department of the University of Louisiana, also reported excellent results from the use of lemons in pellagra

A study of dietary habits of pellagra patients before they developed the disease is convincing that there is marked deficiency of the antiscorbutic vitamin, but it is unnecessary to prescribe synthetic ascorbic acid in the treatment of pellagra Certainly adequate quantities of vitamin C may be administered in raw fruits, oranges and lemons in particular, fruit juices, and raw vegetables Canned tomato juice and canned tomatoes, which are cheap, are rich in utilizable ascorbic acid

Vitamin Crazy—In the November, 1938, number of *Hygeia*, published by the American Medical Association, there is an article by Lois Mattox Miller, entitled "The Vitamin Follies," in which she voices the opinion of many thoughtful physicians She says

"In the opinion of the medical profession the American people have gone 'vitamin crazy' Victims of the latest health fad they gulp quantities of vitamin pills and capsules to prevent colds to ward off a long list of dread diseases to give them pep beauty and strength The family washes with vitamin soap and milady may rub vitamin cream into her skin to 'nourish the skin cells and bring back the blood of youth' Children chew vitamin gum

'In drug store sales vitamin preparations have leaped from tenth to third place and in the words of one trade paper are already eating big chunks from the sales of rival laxatives cough and cold groups' Manufacturers have learned that their drug cosmetic or food products will sell faster if they are labeled as 'containing valuable vitamins A B, C, D, G,' etc"

Lois Miller cites good authority in exposing the vitamin fad

"The medical profession's quarrel is with the advertising which creates the impression that vitamins are drug preparations rather than elements in the balanced diets As Dr Nina Simmonds of the University of California School of Medicine reminded the American Medical Association convention last June this type of advertising is 'leading people to depend too much on drug store capsules and not enough on ordinary food from the grocery and butcher shop

The American Medical Association calls this latest health craze shot gun vitamin therapy' and has expressed the opinion that '*even if no* harm results it should not be forgotten that the giving of complex vitamin concentrates often proves to be an economic waste' Just a dignified way of saying Don t be such a sucker

Finally Lois Miller gives advice which should be heeded by physicians when they are tempted by enterprising detail drug drummers to prescribe all kinds of vitamins for every known malady from pimples to pellagra, when she says

Vitamin addicts could save money and still stock up on their vitamins by switching their interest from fad to food Impressively enough it is the doctor (who believes in vitamin pills but knows how and when to use them) who advises that *in most cases you had much better eat your way to health*

A few days before this chapter was written I was in the corner drugstore across from the Clinic offices when a buxom, slightly overweight woman, who appeared in perfect health,

called for brewers' yeast The show windows of this drugstore were filled with advertisements of concentrated vitamins The druggist said that the sale of preparations containing vitamins had increased enormously When asked what proportion of his sales of vitamin preparations were sold "over the counter" and on physicians' prescriptions, he replied "We sell ten times as many vitamins to the public as we dispense on doctors' prescriptions"

Gullible Doctors—Physicians have been victimized by "high powered" detail drug salesmen into prescribing all kinds of vitamin concentrates under various patented trade names, and their patients tell all their friends about the new vitamins, and they go to drugstores and buy them over the counter Unscrupulous, patent medicine manufacturers, who prey upon the credulity of a gullible public, have flooded the market with all kinds of vitamin preparations, and by advertisements in newspapers magazines, and over the radio, the public has been exploited to such an extent that millions of people are taking concentrated vitamins Most of the victims of the propaganda for the use of vitamins should be spending the little money they have for food and not waste it on worthless high priced preparations bought in drugstores

Williams and Spies called attention to the variable vitamin B_1 content of commercial products, including yeast, said to contain the concentrated antineuritic vitamin In examining many preparations, they found some of them worthless and others of variable vitamin B_1 content The by product yeast showed varying degrees of potency while the yeast grown under standardized conditions was more constant in thiamin content They recommend the use of synthetic vitamin B_1, thiamin chloride, the potency of which has been determined Thiamin has been placed on the market by a number of reliable pharmaceutical manufacturers

Sales Resistance—A great need in this country today is to teach the public that nine tenths of the patent medicines, including those said to contain vitamins, sold in drug and department stores are worthless and are advertised fraudulently It is encouraging to note that the Federal Trade Commission has stopped, or has curtailed, the advertisements over the radio of

some of the most blatant and unscrupulous yeast manufacturers who could not substantiate their claims. It is also important to teach the public that in all but a few cases the needed vitamins may be obtained in adequate quantities in various common and inexpensive foods.

Undoubtedly there is a place for vitamin therapy in pellagra, as in many other diseases. It, therefore, is unfortunate for the public to be duped and disappointed in the use of self prescribed vitamins. Williams and Spies, in their valuable book on vitamin B_1 in discouraging the indiscriminate prescribing of vitamin B_1 (thiamin chloride), said: "Its widespread unwarranted use will lead to disappointment and will likely cause this type of therapy to fall into disrepute."

The same danger lies in prescribing nicotinic acid for pellagra and many other maladies on the "hit or miss" principle. It may be added that the physician who is familiar with the vitamin content of various foods is the one who prescribes the least of high priced, commercial, vitamin concentrates.

CHAPTER XXXI

TREATMENT OF SYMPTOMS AND COMPLICATIONS

Stomatitis—The use of nicotinic acid will clear up the mouth lesions of pellagra in a few days but often oral sepsis due to other causes requires treatment In the cases in which there are mild lesions, or an apthous stomatitis, the compound liquid antiseptic (National Formulary) is more effective and less expensive than similar mild antiseptics sold under various trade names One or two teaspoonfuls in a glass one third full of water and used as a mouthwash four or five times a day has seemed helpful *Vanderhoof, of Richmond, in 1916, called attention* to how quickly mouth lesions will clear up following the use of sufficient dilute hydrochloric acid The mouth symptoms usually subside in a few days without medicines when the pellagrin has been placed on an adequate diet

If there are deep seated ulcers in the mouth, touching them with a 10 per cent solution of silver nitrate once a day will hasten their healing

It should be remembered that the mouths of a considerable proportion of the patients with severe cases of pellagra become secondarily infected with the Vincent's spirillum, and that "trench mouth" may be a complication of pellagra In such cases a paste of perborate of soda swabbed in the mouth, or the use of a strong solution of the perborate of soda used as a mouthwash, generally will clear up the secondary Vincent's infection in a few days The use of nicotinic acid for a few days usually will cause the Vincent's spirillum to disappear from the mouth without local treatment

It is not advisable to use mouthwashes, or local application to the tongue and oral cavity in pellagra, if it can be avoided *It also is best to discontinue the local treatment of the mouth* as soon as the lesions heal, because the pellagrin often has his attention fixed on the mouth symptoms and the sooner his mind can be diverted from his *mouth the better it is for the patient*

Gastric Symptoms—As a rule, dilute hydrochloric acid is the only drug indicated in the treating of the bizarre gastric symptoms of which pellagrins complain The quicker the pellagrin

can be persuaded to disregard his stomach symptoms, the sooner they will clear up. In some cases, however, the pellagrin's gastric complaints must be treated. Small doses, 10 Gm., of the strontium bromide, with 10 drops of the tincture of belladonna or one minim of fluidextract of hyoscyamus, in water three times a day before meals for two or three weeks, will be helpful temporarily in ridding the pellagrin of his gastric neuroses. The belladonna is helpful also in controlling the excessive salivary secretion often seen in pellagra. The following prescription, given for two or three weeks to the pellagrin for the gastric neuroses has proved helpful in many cases:

Strontium bromide	oz. i
Fldext. hyoscyamus	dr. i
Aqua q.s. ad	oz. vi

M. & Sig.: Teaspoonful in water before eating three times a day and every 2 or 3 hours if necessary for gastric discomfort.

Nausea, without vomiting, occurs frequently in pellagra. It usually will subside after a few days on a proper diet. If not, the prescription of strontium bromide and hyoscyamus usually will allay the nausea.

Vomiting usually is a late symptom of pellagra, and it will generally subside without medicines, but if the nausea persists, complete rest for the stomach and the use of 50 mg. doses of nicotinic acid intravenously in 1,000 c.c. of a 10 per cent dextrose in saline solution, or Ringer's solution, every eight hours for one or two days will relieve the emesis.

Constipation.—Constipation in the early stages of pellagra usually can be corrected by dietary management, and psychotherapy, but if drugs are needed for constipation the strong purgatives like calomel, cascara, aloin, etc., should be avoided. Perhaps the best laxative in pellagra is mineral oil in from one-half to one ounce doses at bedtime, gradually reducing the dose until the patient has established regular defecation habits. Compound licorice powder in teaspoonful doses stirred in water at bedtime is a mild laxative which has been found useful in treating constipation in pellagra.

Diarrhea.—Nicotinic acid will stop the diarrhea in the average case of pellagra in a few days, but sometimes diarrhea in

pellagra is due to achylia Gastrogenic diarrhea seen often in pellagrins usually will subside when the pellagrin is given dilute hydrochloric acid in from one to one and one half tea spoonful doses in milk with meals and three hours after meals If not, bismuth subnitrate in teaspoonful doses stirred in a glassful of water three times a day, and every two or three hours if necessary, will check bowels in many cases If the pel lagrin is in the hospital and the diarrhea is severe, a hypo dermic of one fourth grain of morphine once or twice a day generally will control it Tincture of opium in 10 drop doses, or paregoric in teaspoonful doses, may be given in severe diar rhea, which cannot be controlled without opium but the pella grin should be cautioned not to use it except for a few days

Colonic irrigations have not been found helpful in the diar rhea of pellagra, but if there is discomfort in the rectum, with more or less constant desire for the bowels to act, an enema of one half to one pint of warm salt solution usually will relieve the tenesmus A soft rubber catheter attached to the small hard nozzle of a fountain syringe should be used in giving enemas

Boggs uses calcium chloride in gram doses, intravenously, in intractable diarrhea, with good results generally, but says that it has failed in some cases

Sometimes in beginning the treatment of pellagra and at any time, when the diarrhea is uncontrollable, total abstinence from all food for from twenty-four to forty eight hours and use of nicotinic acid in 1,000 c c of a 5 or 10 per cent dextrose in saline solution every eight hours will stop the excessive purga tion At the same time a transfusion of blood should be given and repeated every few days if the diarrhea cannot be con trolled and the patient is prostrated and emaciated

Dermatitis—The uncomplicated skin lesions of pellagra usually require no local treatment In many cases the pellagrin will complain of a burning sensation of the hands and feet, but it is not unbearable and many physicians have observed that local applications exaggerate rather than relieve the burning The skin lesions in the uncomplicated cases will clear up in a few days of treatment with nicotinic acid The use of local appli

cations centers the pellagrin's attention to his hands and feet The compound calamine lotion with 1 per cent phenol applied to the lesions once or twice a day has proved helpful in cases with secondary infections Greasy preparations and ointments should be avoided, because their use adds to the difficulty of keeping the lesions clean

The daily warm bath adds to the comfort of the pellagrin, and no doubt prevents secondary infection of the skin lesions When there is a secondary infection with pyogenic organisms, as in the wet type of skin lesions, daily dressing and treatment as an infected wound are indicated

Neuritis —In occasional cases associated with neuritis, pains particularly of the feet and legs sometimes of the hands and arms, may occur 5 or 10 gr doses of aspirin in the milder cases of peripheral neuritis usually will give temporary relief Warm, but not hot, baths are helpful to relieve the pain Spies has found that large doses of thiamin hydrochloride will clear up the neuritis in a few days In the severe cases of peripheral neuritis morphine may be required for a few days until the specific effect of nicotinic acid is obtained

Drugs —Goldberger's statement that "there is no specific drug in the treatment of pellagra " is true, and he was right in maintaining that diet is essential in preventing and curing the disease, yet medicines, when indicated to combat symptoms as they arise, are important adjuncts in the treatment of the pellagrin

Hydrochloric Acid —Next to nicotinic acid the one most important drug in pellagra is dilute hydrochloric acid In the mild cases, in which an examination of the pellagrin's stomach contents shows normal degrees of gastric acidity, there is no necessity for giving dilute hydrochloric acid Since in at least 90 per cent of cases there is either hypochlorhydria or achlorhydria, if the physician is not equipped to analyze the gastric juice, he should use dilute hydrochloric acid in the treatment of his cases of pellagra

The dilute hydrochloric acid is best given in doses from one to one and one half teaspoonfuls (4 to 6 c c), stirred in milk, with meals and three hours after meals The patient should be told that sometimes the hydrochloric acid will curdle the milk

but that is the first step in digestion of milk, he should stir the milk and drink it even if it does curdle

Physicians formerly did not give enough dilute hydrochloric acid I have had pellagrins, whose stomach contents showed no free hydrochloric acid present, take one and one half tea spoonful doses of dilute hydrochloric acid in milk five times a day for years and continue in perfect health If the pellagrin cannot get milk, the dilute hydrochloric acid may be given in a glass full of water, with instructions to take it through a glass tube The dangers to the teeth from using hydrochloric acid are exaggerated, but if a glass tube is not available when the acid is taken in water, the mouth may be rinsed out with a solution of plain baking soda, one teaspoonful to a glass of water

Sedatives—Sedatives of all kinds, particularly the barbitu rates, should be avoided as much as possible, in the treatment of pellagra It is surprising how quickly the nervous symptoms of pellagra will subside when the patient is placed at rest on the proper diet, with feedings between meals and every two or three hours if awake at night Psychotherapy, by assuring the pellagrin that he can and will get well, provided that he will be patient and do his part, will do much to relieve the anxiety and mental depression so frequently found in pellagra

The barbiturates may be helpful occasionally, but they often add to the depression of the pellagrin, and when used to ex cess, or over long periods of time, they may produce a toxic delirium which may be mistaken for an actual psychosis I have seen several cases in which a mild delirium would clear up when the barbiturates were stopped

It is particularly desirable to avoid using the barbiturates to produce sleep, because the following day the pellagrin is more depressed from the use of the drug than he would be if he had lain awake all night If any barbiturates are considered neces sary U S P phenobarbital is as good as any of the more ex pensive drugs of that class The fact is that the barbiturates with patented trade names are essentially the same thing as phenobarbital

If a sedative is necessary, small doses of strontium or sodium bromide are more dependable and less depressing than the bar

biturates Ten grains three times a day will control most of the nervous manifestations of pellagra, and the bromides should be discontinued as soon as possible, because pellagrins are prone to become dependent upon drugs I have never seen a pellagrin who had formed a drug habit, but such cases have been reported

Occasionally in the severe cases of pellagra complicated with an active delirium, it may be necessary to use a narcotic, and morphine in one fourth grain doses given hypodermatically is the most dependable of the opium derivatives Morphine or the deodorized tincture of opium may be necessary to control severe diarrhea in pellagra

Treatment of Complications—Pellagra is usually a chronic disease, and pellagrins often consult physicians for other diseases, when they are found upon examination to have pellagra and syphilis, or pellagra and amebiasis, or uncinariasis, or arteriosclerosis, or cancer, or alcoholism, or any one, or more, of a hundred diseases which have been observed associated with the disease In treating the complications of pellagra the dietary management and the use of drugs as indicated from the symptoms may be carried out pari passu with the treatment of the complicating diseases

In many cases of pellagra a preceding disease is the primary or a contributing etiologic factor, and with appropriate treatment of the complicating disease, the removal of the cause, the patient will recover without any treatment directed toward the cure of pellagra Many cases of pellagra, associated with amebiasis and infestations with Giardia and various other intestinal monads, have been reported cured by treatment directed toward the eradication of the intestinal protozoa In cases of alcoholic pellagra, the oral, intestinal, and skin symptoms usually will subside in a few days after the pellagrin discontinues the use of beverages containing ethyl alcohol

Treatment of Syphilis in Pellagrins—The treatment of syphilis in a pellagrin may clear up the syphilitic manifestations and cure the pellagra Perhaps some of the cases in which the use of arsphenamine has cleared up the oral, gastrointestinal, and skin lesions of pellagra "like magic" have been in patients whose pellagra was secondary to syphilis Certain it is that syphilis and pellagra exist together in many cases In

such cases, the victim is in a lowered state of vitality from the syphilis, and from avitaminosis It seems probable that syphilitic liver damage, causing hepatic insufficiency, may be the primary factor in producing nicotinic acid deficiency

It would seem advisable in the treatment of primary or secondary syphilis, in a pellagrin, to begin with a small dose of arsphenamine, one tenth of a gram, and increase the dose by one tenth gram if no reaction occurs Except in the very mild cases of pellagra in chronic syphilitics, it is best not to use arsphenamine because of its occasional toxic effect on the liver Instead, bismuth subtartrate in gram doses, injected deeply into the gluteal muscles, should be used for a few weeks or months before beginning neoarsphenamine intravenously

Potassium iodide is a valuable adjunct in the treatment of tertiary syphilis, and the great majority of syphilitic pellagrins need that drug for several weeks or months before beginning any arsenical intravenously Potassium iodide is best given in 25 gr doses in a saturated solution, 25 drops in a full glass of water after meals, three times a day

The United States Public Health Service, cooperating with a group of clinicians in charge of syphilis clinics in a number of leading medical schools, has standardized the treatment of syphilis Every physician in the United States should be familiar with the outline of treatment for syphilis adopted by the Cooperative Clinical Group Upon application to the United States Public Health Service any physician may procure a detailed outline of the treatment of syphilis as advised by the leading syphilographers in the world

It would seem to be more important for the adequate treatment of syphilis to be carried out with a pellagrin than in an uncomplicated case of syphilis The course of treatment for syphilis advised by the Cooperative Clinical Group should be carried out with the syphilitic pellagrin after his recovery from pellagra, and after several weeks' or months' use of treatment with bismuth and potassium iodide

Tuberculosis—In the case of the pellagrin who has tuberculosis the same diet is indicated for both diseases, and it has not changed in nearly two thousand years when Aretaeus, a Gre

can physician, said "In tuberculosis milk sufficeth both as food and medicine" and he extolled the value of "fresh laid eggs," as the modern nutritionist insists that the vitamin content of eggs deteriorates each day

Pneumonia—*Pneumonia is often the friend of pellagrins, as Osler said it is of old men, by taking them out of their misery* Certainly the mortality of pneumonia is high among pellagrins No doubt the use of sulfapyridine will reduce the mortality of pneumonia complicating pellagra Early and repeated blood transfusions in pneumonia complicating pellagra and the use of nicotinic acid in dextrose in saline solutions may tide the pellagrin through the attack Thiamin chloride in large doses parenterally may be helpful in preventing and controlling the vitamin B deficiency in the pellagrin who has pneumonia

Secondary Pellagra—Pellagra secondary to inoperable cancer, ulcerative colitis and other usually fatal maladies, may be benefited but not cured by transfusions, liver diet, or liver extracts, the use of thiamin chloride and nicotinic acid, parenterally, and by mouth

Surgery in Pellagra—Since pellagrins are poor surgical risks, in cases complicated by gall bladder diseases, gallstones, neglected ulcer of the stomach or duodenum, or other surgical condition, intensive treatment of the pellagra should be carried out if possible, before any operative procedure is undertaken Repeated blood transfusions and the use of liver extract, thiamin, and nicotinic acid, parenterally, are indicated in preparing a pellagrin for operation and in the postoperative management of the case

Psychotherapy—Unfortunately the impression prevails that treating pellagra consists in giving yeast, or nicotinic acid, and good food a fallacy that has been productive of self treatment by the pellagrin, who buys yeast or nicotinic acid tablets or gets it from the health department and tries to diet himself Pellagrins say "*What is the use of seeing a doctor? He cannot do* anything for me except to give yeast, or nicotinic acid, and tell me *what to eat*" Besides, *the impression that the treatment of* pellagra consists of giving yeast, or nicotinic acid, and an adequate diet begets carelessness among physicians in treating pellagrins

The fact is that there is no disease which requires greater therapeutic skill to cure the patient than pellagra It is true that the symptoms in mild cases will subside when the patient is properly dieted, either with, or without, the use of yeast or nicotinic acid, but he is not cured until the physician has made a careful study of the pellagrin's environment and his habits, particularly as related to food, and then has taught his patient to regulate his life, including instructions regarding the use of nutritious foods rich in vitamins, so that he will not have a recurrence of his disease

Regulate Life of Pellagrins —Weir Mitchell, the great neurologist who gave the "rest cure" to the medical profession, once said "The best doctors of all time have been those who regulated the lives of their patients so that they may be restored to, and maintain, health" Certainly the best doctor for the pellagrin is one who does not confine his treatment to any therapeutic fetish, or fad, but who studies each individual patient, and finding the cause of his malady removes it, and then teaches his patient how to so live that he can regain, and retain, his health

Re educating the Pellagrin —I will take this opportunity to express my gratitude to Dr Llewellyn F Barker for teaching me the importance of psychotherapy in the treatment of patients suffering from a large variety of diseases In 1906, during six months of post graduate study at Johns Hopkins, I had the *privilege of making daily "ward rounds" with the senior class* of students in the Johns Hopkins Medical School Day after day Dr Barker stressed the importance of psychotherapy until "re education of the patient and regular systematic encouragement" became a fixed habit of thought with me in dealing with every patient without regard to the nature of his ailment so long as there is any hope of improvement *in the patient's condition*

On the advice of Dr Barker, I purchased and read, and re read several times, DuBois' book on *The Psychic Treatment of Nervous and Mental Disorders* and DuBois' little book entitled *The Influence of the Mind Over the Body* Dr Barker did not mention psychotherapy in pellagra, because up to that time (1906) there had never been a case diagnosed as pellagra

in the Johns Hopkins Hospital, but the next year when I was called upon to treat many cases of pellagra, I found that the principles of psychotherapy as discussed by Dr Barker and laid down by Paul DuBois in his books, applied to pellagra as much as to any other disease in which the anxiety neuroses are factors in the discomfort of the patient

Dr Barker also stressed the value of the Weir Mitchell rest cure, of which "forced feeding" is an important feature, in functional nervous diseases in which undernutrition is a factor It may be added that, without exception, every physician in the South who published papers on the treatment of pellagra for the first ten years after it was found to be endemic in the Southern states, mentioned undernutrition as a factor in pellagra and stressed the importance of a full diet in the management of the disease

It also may be added that the best doctor for the pellagrin is the one who knows something of psychology, and in addition to using drugs and diet, as indicated, practices psychotherapy The fact is there are many physicians whose success depends largely upon psychotherapy, which they sometimes practice without realizing that the confidence of the patient, particularly the depressed pellagrin is "half the battle" in securing the cooperation needed in the management of chronic cases of pellagra

One of the ablest of American physicians, and one of the three or four greatest clinicians in the history of pellagra in the United States, was Dr J W Babcock of Columbia, South Carolina Dr Babcock at the time he read a paper on the treatment of pellagra at the meeting of the Southern Medical Association in 1916, probably had treated more cases of pellagra than any physician in the United States The Weir Mitchell "rest cure," including psychotherapy, was the basis of Dr Babcock's treatment of pellagra, and no abler discussion of the treatment of pellagra has ever been published than the paper by Dr Babcock in the *Southern Medical Journal* in May, 1917 The principles of treatment outlined by Babcock have not been improved, and they apply in 1940 as they did thirty years ago, when Babcock and others began using a modified Weir Mitchell rest cure, which included forced feeding, in the treatment of pellagra

The Sunlight Hazard.—The physician who is treating a pellagrin should not fail to explain to him that exposure to sunlight before he has been cured completely not only may bring on a return of the skin lesions of the face, neck, hands, and other exposed surfaces, but it may cause an exacerbation of the mouth, gastrointestinal, and nervous symptoms. My failure to impress a convalescent pellagrin, who believed that he was well, with the necessity for keeping out of the sun for at least the rest of the summer was responsible for one of the few deaths from pellagra in thirty-four years' experience in treating the disease. This patient, a banker, after a month's stay in the hospital, on returning to his home drove 20 miles in an open buggy, following which the skin lesions, diarrhea, and mental depression returned. A few days later he committed suicide. This experience taught me a lesson which I have not forgotten, and since then I have tried to impress every pellagrin I have treated with the importance of keeping out of the sun from April to November for one or two years after recovery from active symptoms of pellagra. Since 1910, only a very few cases can be recalled in which there was a recurrence of symptoms in recovered pellagrins.

C. C. Bass, in *1910*, stressed the importance of *instructing* pellagra patients to avoid exposure to sunlight for two or three years after recovery. In April, 1940, W. J. Aycock, a general practitioner of Mississippi, said that he formerly had so many recurrences among his recovered pellagrins following exposure to sunlight, that for many years he had instructed them to wear wide-brimmed straw hats and white cotton gloves when in the open air from early spring to late fall for two or three years after recovery. Many other physicians of large experience in treating pellagra have learned the lesson to teach their pellagrins to protect themselves against exposure to sunlight for several years after recovery.

I believe that many cases of pellagra may be prevented in the rural districts in which endemic pellagra prevails if physicians would instruct the other members of a household in which there is a case of pellagra to wear wide-brimmed straw hats and cotton gloves while working in the fields from early spring to late fall. Public health officials and public health nurses

should teach all the people in districts in which endemic pellagra prevails, and where there are many potential, or borderline, cases of pellagra, that exposure to sunlight of persons predisposed to pellagra may precipitate an acute attack, with the dermatitis, oral gastrointestinal and nervous symptoms

It is true that not every convalescent pellagrin will have a recrudescence of symptoms after exposure to sunlight, and that not every case of pellagra has a history of sunlight as a precipitating factor in bringing on the disease, but the researches of Ruffin and Smith show that a large proportion of patients who have had pellagra will have relapses if exposed to the sun It, therefore, is evident that the sunlight factor should not be forgotten in the prophylaxis and treatment of pellagra

Effects of Sunlight on Potential Pellagrins—If the physician who treats borderline food deficiency conditions, including potential pellagra, or subclinical pellagra, will instruct his patients to keep out of the sun as much as possible for a year or two after treatment, he will prevent some of them from developing the skin lesions, and an increase of the oral, gastrointestinal, and nervous symptoms of pellagra In the last two years because of failure to instruct potential pellagrins to keep out of the sun, three ambulatory patients who were being treated in the Seale Harris Clinic developed the classical triad of symptoms i e, dermatitis, diarrhea, and depression

One patient, an intelligent woman, who had been operated upon for gallstones, came under observation in January, 1938 While on a pellagra preventive diet in June, 1938 after working in her garden in the sun, she developed the typical skin lesions on the backs of her hands, and at the same time her tongue became sore and reddened, and she developed diarrhea Her symptoms cleared up promptly with the use of nicotinic acid and liver Pellagra had not been suspected in this case until after exposure to sunlight brought on the skin lesions and exaggerated her mouth and other symptoms

The condition of another patient, a young woman whose principal complaint was diarrhea and sore mouth but who had no skin lesions, had been diagnosed as subclinical pellagra or endemic sprue After exposure to the sun in the spring of 1939, she developed the typical skin lesions of pellagra on the top of

her feet and on the front of her legs halfway up to the knees She had worn slippers and no stockings She was given nicotinic acid and Valentine's aqueous extract of whole liver residue She lives in the country about 100 miles from Birmingham and has not been heard from since she was given antipellagra treatment, but it is presumed that she recovered promptly as many other similar cases have done

A third case, in which pellagra had not been suspected, was an undernourished girl who had spontaneous hypoglycemia A glucose tolerance test gave a typical hyperinsulinism curve Her diet, while not prescribed as pellagra preventive, was rich in all the vitamins In the summer of 1939 after exposure to sunlight, wearing slippers but no stockings, she developed a typical skin lesion of pellagra on her feet and legs, the line of demarcation of the lesions being where her feet were covered by her slippers Her symptoms cleared up promptly under treatment

Completing the Cure of Pellagra —The physician should study the habits and the environment of his pellagra patient, and finding the contributing causes, as fatigue, *insufficient or improper food*, insanitary surroundings, and alcoholism, he should instruct him regarding the things that he can do to prevent a recrudescence of his symptoms He *should have the patient* report to him once a month during the summer and autumn of the first year he has been under observation, and again each *spring and summer for two or three years, for examination and* for further instructions regarding his food and personal hygiene, and, what is just as important, for regular, systematic encouragement When *the pellagrin comes back every month* or two for a check up, he should not be dismissed with a look at his tongue and by feeling his pulse and telling him that he is all right, the physician *should make a thorough examination* of the patient He then will hold the confidence of the pellagrin, and can teach him more effectively that he cannot go back to his way of living *when he developed pellagra if he would hope to* enjoy health, efficiency, prosperity, and long life

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Author's Note —Medical literature has been enriched by the several thousand articles on pellagra which have been published since the disease was found to be endemic in the United States in 1906 I have not read all of the articles on pellagra that have appeared in text books medical encyclopedias and medical journals, though I collected the bibliography of at least 5,000 references I have endeavored however, to review many of the most important articles on pellagra published since 1906, and have prepared a working bibliography which was used in the preparation of my 26 chapters on *Clinical Pellagra* It was found that if the bibliography were placed at the end of each chapter there would be many duplications, which would add to the length of the book For this reason the working bibliography appears after the last chapter It is hoped that others may find this bibliography useful in the preparation of papers and in their studies and investigations on pellagra

Listed in this bibliography are articles written by physicians in nearly every state in the United States which show that pellagra is a national problem Titles of many articles published by American and foreign physicians have been omitted In fact more than nine tenths of the references to pellagra collected from medical literature have been deleted in making up a working bibliography

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INDEX

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